

CURRENT OPINION

Re-evaluation

Current problems in the laboratory diagnosis of cervical cancer

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USEFUL laboratory techniques must be simple, accurate, and reproducible. In the study of cancer the most crucial criterion and the one in which all current laboratory methods are deficient is a sharp end point. These methods are best categorized as biochemical, morphologic, and histochemical.

There have been a large number of biochemical tests for cancer.^{9, 11, 16, 18, 21} Those performed on blood samples usually depend on nonspecific changes in serum proteins.²¹ Whether the cancer is responsible or develops secondarily is not known. Blood and cancer tissue assays create optimistic interest for brief periods, but, because inflammatory and other nonspecific components contribute as variables, none of these methods have been satisfactory with regard to end point.

Fluorescent dyes are now used to stain tissue sections and smears in which malignant cells fluoresce markedly under ultraviolet light.²¹ Other methods using fluorescein globulin complexes leave malignant cells differentially unreactive. However, an analysis of photographs, accompanying current re-

ports of microfluorescence, leaves inconclusive the fluorescent activity of benign anaplastic cells. In one recent report of cervical cancer it was acknowledged that adjacent histologically innocent tissue did show patchy areas which stained like cancer.²⁰ These areas the author considered precancerous.

Microfluorescence occurs when a specific cytologic antigen is reacted with fluorescein labeled specific antibody. Another method first involves the deposition of unlabeled specific antibody over the cell. This step is followed by the addition of fluorescein-labeled antibody against the deposited unlabeled gamma globulin antibody attached to antigen. No specific antigen or antibody for cancer is known. Reports of differential microfluorescence in malignant material have involved gradients of fluorescence of non-specific material such as ribonucleic acid and desoxyribonucleic acid. Increase of these has been repeatedly shown to reflect growth and cell division but not cancer per se. Even though fluorescence may ultimately demonstrate a sharper end point than current cytologic screening it provides no specific reaction for cancer.

In regard to cytomorphologic studies, the Papanicolaou method is empiric but nonetheless retains considerable practical value

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in screening for cancer. However, observations such as described in precancer patterns involve very subtle and controversial cytologic alterations.² While this is currently widely debated and probably important, much time will be necessary for us to appreciate and to evaluate these patterns. At present the end point in cytomorphology remains far from simple and the mainstay of definitive diagnosis remains histomorphology.

Because of practical need to delineate differences between borderline cases, attention is being directed more and more toward fine nuances of morphologic variation. Indeed, histologic data have become so highly refined and reports from even acknowledged scholars in the field are so often ambiguous that one may justifiably wonder if carcinoma in situ is a valid diagnosis and, if so, what criteria protect this diagnosis. Because haziness in nomenclature alone has added to the con-

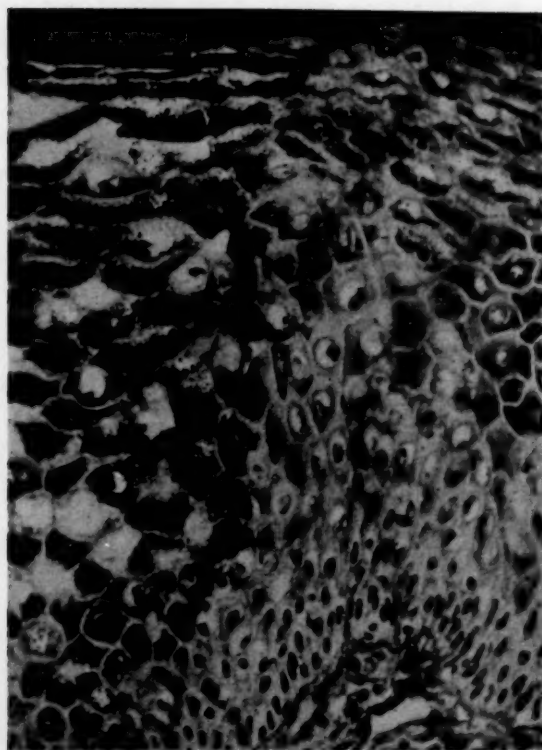


Fig. 1. Leukoparakeratosis. Periodic acid-Schiff reaction. Note the abrupt change between the PAS-positive mature cells of the normal area on the left and the negative or weakly positive immature cells in the leukoparakeratotic focus on the right. ($\times 500$.) (From Gross and Danziger.¹²)

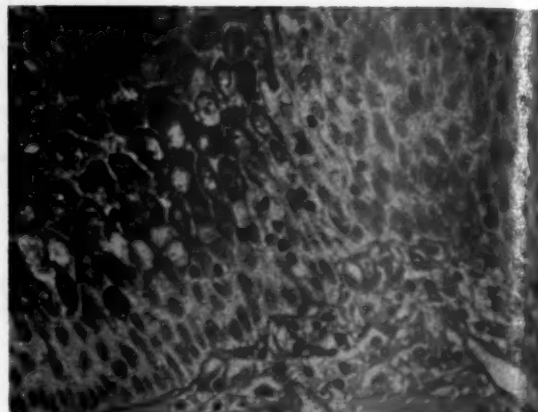


Fig. 2. Carcinoma in situ. The change between the normal area on the left and the malignant zone on the right is abrupt. Compare this with Fig. 1. The PAS-negative cells of the carcinoma in situ appear very similar to the basal cells of the normal area. ($\times 500$.) (From Gross and Danziger.¹²)

fusion and because we must have a base line of terminology before histochemical data can be understood, it is wise to define arbitrarily some descriptive terms relative to histomorphology of the cervix.

Epidermidization. This consists of growth of squamous epithelium from the portio to cover a congenital or acquired erosion. The columnar cells of the surface and underlying endocervical glands are replaced by squamous cells with normal polarity and few mitoses. This is not a premalignant lesion.

Squamous metaplasia. The squamous type cells constituting this alteration are derived from the "reserve" cells beneath the surface. They proliferate and impinge on the superficial columnar epithelium which usually remains well preserved. Columnar cells lining stromal glands are replaced and occasional gland lumina are filled by these cells. For practical purposes, epidermidization may be diagnosed when the squamous alteration is seen to proceed upward from a visible squamous surface and squamous metaplasia when there is a columnar surface over involved stromal glands.

Epidermoid hyperplasia. This is the downward stromal extension of large rete pegs, each of which retains a regular layer of basal cells.

Hyperkeratosis. In this benign alteration the squamous epithelium produces an homogenous surface layer of keratin without nuclei.

Parakeratosis. This is also characterized by marked keratin production in the surface cells, but nuclei are retained.

Paraleukokeratosis or leukoparakeratosis. This is characterized by an abrupt, almost vertical line of demarcation between mature glycogen containing cells and immature cells without glycogen. The latter do not stain in the Schiller test. However, this lesion is benign and is not premalignant (Fig. 1).

Anaplasia. Anaplasia is most purely defined as immaturity or lack of differentiation. However, in the recent literature concerning lesions of the cervix, anaplasia has been broadened to include several concomitant but perhaps independent features. In other tissues anaplasia does not present these features. For example, anaplastic endometrial glands have no increased mitoses, no loss in polarity, and no hyperchromatic nuclei.

Basal cell hyperplasia. The lower one third or one half of the squamous epithelium is anaplastic, but the upper portion is mature. In current common usage anaplasia of the cervix consists of an advanced form of basal cell hyperactivity which can involve almost the entire thickness of the epithelium.

Carcinoma in situ. In its purest form carcinoma in situ looks like unequivocal cancer. The epithelium has the same appearance as the surface spread from invasive cancer which is aptly designated "sugar coating" in German reports.²⁶

A typical carcinoma in situ can nearly always be diagnosed histologically^{8, 35} (Figs. 2 and 3). However, there are borderline cases where carcinoma in situ can be confused with anaplasia. In such cases morphologic criteria provide an inadequate end point.³³ McKay recently summarized these features.²⁴ His succinct description of anaplasia of the cervix includes the following epithelial alterations: "The usual arrangement of cells is disturbed. There are mitoses and often multinucleated cells in the superficial layers. Many nuclei are enlarged, irregular, and hyperchromatic." However, a thin surface layer of mature cells persists in anaplasia. Confusion is provided by some authors who claim that anaplasia is the same lesion as basal cell hyperactivity, basal cell hyperplasia, atypia, dysplasia, benign atypia, squamous metaplasia, and leukoparakeratosis.²⁵ However, arbitrary distinctions usually can be made and are required for precise follow-up data. By this approach we have learned that squamous metaplasia and leukoparakeratosis are not precursors to cancer but that anaplasia can be.^{10, 33, 35}

Depending on criteria and degree of change in anaplasia, 2 out of 3 patients will eventually develop carcinoma in situ according to Galvin,¹⁰ but only 2 out of 10 according to McKay.²⁴ While carcinoma in situ is diagnosed occasionally despite a persistent thin surface layer of mature cells, the safest morphologic criteria for this lesion at present consists of marked anaplasia extending to and including the surface. Indeed there are even instances where only the surface cells

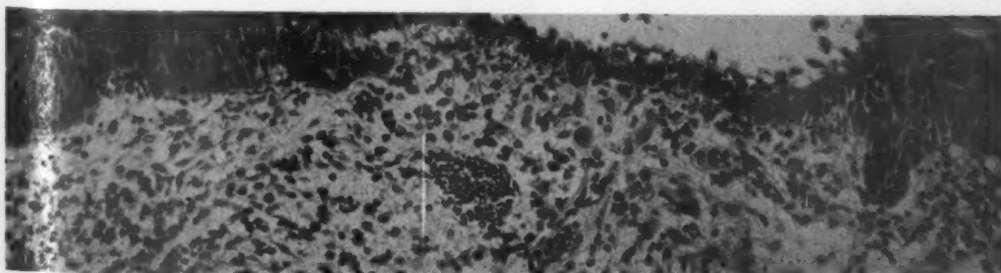


Fig. 3. Carcinoma in situ. Note surface extension of undifferentiated malignant squamous cells gradually replacing columnar cells. (Hematoxylin and eosin. $\times 192$.)

are involved.³⁵ Strict criteria will help at least to eliminate overdiagnoses which tend to undermine our faith in the very validity of the *in situ* concept. The fact that there may be anaplasia, carcinoma *in situ*, and even invasive cancer at different foci of a single specimen complicates diagnostic as well as follow-up studies. Many blocks and often more sections are required than is practicable. Furthermore, if an adequate specimen is removed, the patient may be cured and unsuitable for further study. On the other hand, it is often difficult to know if unremoved epithelium retains skip areas of unsuspected disease.

In the past 10 years these various problems have been indirectly responsible for published data which cast doubt on the validity of carcinoma *in situ* as a biologic entity. Apart from those of spontaneous remission, there have been periodic reports of cures of carcinoma *in situ* by various topical agents.¹ Nonspecific irritants such as trichomonas, urethane, colchicine, and podophyllin have produced changes in the human cervix allegedly identical with those of carcinoma *in situ*.^{3, 20} While supportive photomicrographs do show atypia, hyperchromasia, loss of stratification, large nuclei, and bizarre mitoses, the alterations are not the same as those of carcinoma *in situ*. They do capitalize on the sources of confusion discussed earlier.

It is beyond the scope of this report to document existing evidence for the biologic validity of the *in situ* lesion. Yet, pertinent to the discussion of its morphologic diagnosis, we have had to direct attention to some items which compound the problem. The weakness of morphologic diagnosis is more clearly illustrated by some papillomas of the vulva and leiomyomas of the uterus which appear benign by all morphologic criteria yet metastasize and ultimately kill the patient. Such obvious limitations of morphology plus the increasingly prevalent notion that cancer involves a fundamental alteration in cellular chemistry have prompted new and widespread interest in histochemical techniques.

In 1954, I reported histochemical observations of benign and malignant tissue sections

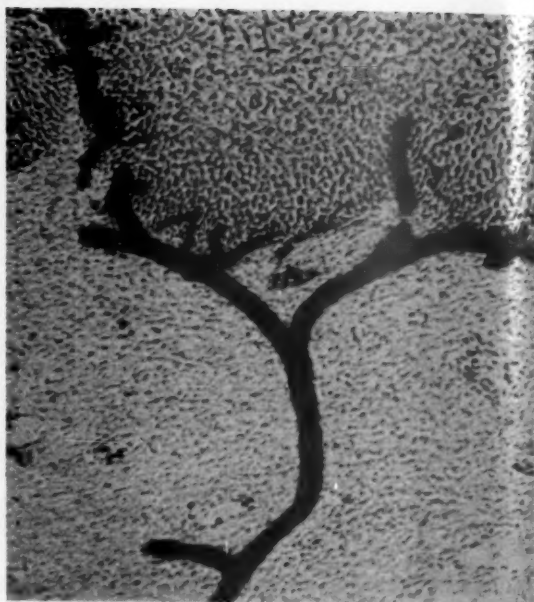


Fig. 4. Alkaline phosphatase. Frozen section of cervix. Squamous epithelium is negative. Note the striking pattern produced by intensely positive vascular endothelium. ($\times 150$.)

of human cervix uteri.¹² A review of the biochemical and histochemical literature at that time disclosed differing opinions and frequent inconsistencies regarding intracellular localization. To minimize previous sources of error, this study emphasized fresh, unfixed frozen tissue sections. One section was stained with hematoxylin and eosin and the neighboring section was reacted chemically. Thereby immediately adjacent sections could be compared for morphology and chemical localization. Reactions and stains were done for ribonucleic acid, desoxyribonucleic acid, glycogen, mucin, lipids, sulfhydryl, disulfide, alkaline phosphatase, acid phosphatase, non-specific esterase, glucuronidase, and phosphamidase. It was decided that the intensity of histochemical reaction of cervical squamous epithelium depends on differentiation and on tissue specificity but not malignancy *per se*. Since that time several reports from other laboratories have confirmed this concept.^{5, 8, 17} Because accurate intracellular localization is often uncertain even in thin tissue sections, it was recently decided to react cytologic preparations. In general, the localization in tissue sections is confirmed by

the cytologic material. A detailed description appears elsewhere.¹⁴

It is of interest that tissue sections in 1954 suggested the absence of alkaline phosphatase in benign and malignant squamous cells although diffusion and nonspecific staining from strongly positive endothelial and inflammatory cells were troublesome (Figs. 4 and 5). Cytochemical data confirmed the absence of alkaline phosphatase in squamous cells.¹⁴ However, a recent tissue study suggested that cervical squamous cells were lightly positive for alkaline phosphatase although it was acknowledged that diffusion from nearby blood vessels might have occurred.¹² Actually, endothelium specifically is involved. Indeed the reaction is so marked that local diffusion in tissue sections is unavoidable. By liberating inorganic phosphates from mononucleotides and ribonucleoproteins, alkaline phosphatase facilitates chemical transfer across cell membranes. In this regard intense alkaline phosphatase activity in capillary endothelium assumes considerable significance. Although squamous cells

reveal no alkaline phosphatase, it must be remembered that current histochemical methods, utilizing hydrolysis of a single simple substrate, may not completely reflect reactions in the cell which contains numerous complex substrates.

Theoretic arguments concerning discrete deposition versus diffuse staining are discussed frequently.^{13, 27} To facilitate accurate comparison between cells, reactions should be manipulated to produce a punctate precipitation. This has provided evidence for a not entirely surprising concept. If the degree of histochemical activity in a given tissue reflects differentiation primarily and if cancer tissue differentiates (however imperfectly), then a similar gradient of chemical activity should also occur in cancer.

It remains puzzling that carcinoma in situ having very immature, rapidly dividing cells with high ribonucleoprotein, acid phosphatase, and nonspecific esterase is slow growing and remains localized for many years while invasive carcinoma often with pearls containing numerous "differentiated" cells with low ribonucleoprotein, acid phosphatase, and nonspecific esterase readily invades tissues, metastasizes, and destroys the patient. Nuclear transformation must play an important role here, but the chemistry remains unknown. While microspectrophotometric analyses show marked variation and increase of nuclear ribonucleoprotein in malignant cells, it has been demonstrated that this is correlated with mitosis and not malignancy per se.^{19, 30} With respect to nuclear chemistry, genes are receiving closer scrutiny. While such an approach seems fundamentally different from one which seeks a specific diagnostic alteration in cancer, it should be emphasized that both trends are closing on the problem in a strikingly similar way. Although viruses have not yet been isolated from human malignant tissue, electron microscope studies have revealed suggestive nuclear particles in leukemia and cervical cancer cells.^{6, 7} It has also been shown that a virus can be made to undergo genetic mutation which alters the chemical activity of its nucleoprotein.³⁴ Another link is pro-

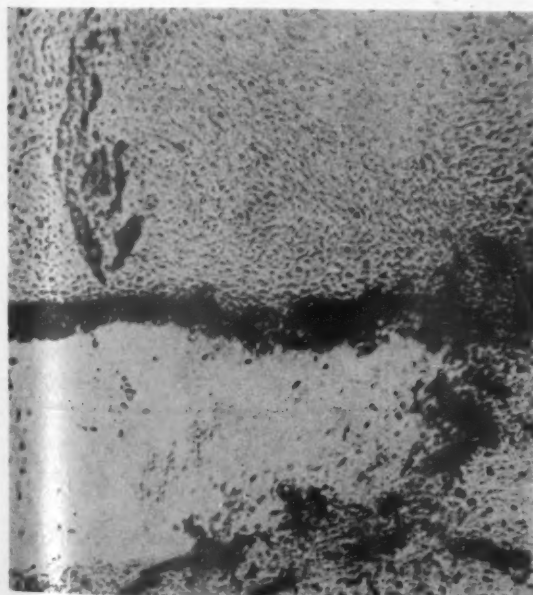


Fig. 5. Alkaline phosphatase. Frozen section of cervix. Normal squamous epithelium is negative. While columnar epithelium of cervical glands frequently shows a true positive reaction, note that intensely reacting capillary vessels surrounding the gland confuse interpretation of adjacent epithelial reaction. ($\times 150$.)

vided by the evidence that a particular enzyme may be absent in a tissue following mutation of the enzyme specific gene.²⁸ Therefore, it is entirely possible that a chronic irritant (e.g., virus) can induce a genetic mutation in the host whereby a crucial enzyme system concerned specifically with cell division is altered.

Apart from diagnostic end point it has long been thought that variations in mitosis and cellular differentiation may provide knowledge of the pathophysiology of cancer. In 1923 Martzloff first considered the morphologic aspects of this problem.²² Later he pointed out that the morphologic cell type in a biopsy does not necessarily reflect the type of the main tumor.²³ Furthermore, experience has shown that the predominant cell type of the tumor does not always correlate with degree of malignancy. Approaching cellular differentiation differently, Caspersson used ultraviolet spectrophotometry to show two types of tumor cells in cervical cancer.⁴ Rapidly dividing "A" cells contained more cytoplasmic ribonucleic acid and nuclear desoxyribonucleic acid than "B" cells which had more cytoplasm and larger nucleoli but were regressive and had finished protein synthesis. Gusberg developed this concept further, stating that the growing edge of a radiosensitive cervical cancer has many "A" cells and a change to "B" cells occurs during successful radiation.¹⁵ Studying proteases of which he found 20 to 30 times more activity in "A" cells than "B" cells, Sylven pondered the possibility of "B" cells becoming transformed into "A" cells if nutritional require-

ments were met.³² This is important and, if possible, should be carefully documented. If "B" cells have completed protein production, do these regressing "mature" cells retain the potential for dedifferentiation and limitless cell division? The latter, after all, is the unique trait of cancer. A thoroughly documented answer should bring us to the very secret of life itself. If some cancer cells such as Caspersson's "B" cells cannot dedifferentiate or cannot continue to divide, perhaps only such cells are present in areas of certain tumors that become stationary or even disappear spontaneously.

Conclusion

Morphologic and chemical studies of cancer thus far have documented only the transformation of undifferentiated cells to differentiated cells. As malignant cells mature, they acquire chemical characteristics similar to maturing nonmalignant cells. Although this transformation is not identical in normal and cancer tissues, it does occur in both and with similar gradients of cytochemical activity. While the chemical spectrum of cancer is slowly becoming clarified, its basic alteration thus far seems independent of morphologic and chemical differentiation. When a specific reaction for cancer does become available, apart from diagnostic considerations, it may tell us more about dedifferentiation and the limits of cell division. Possibly the enigma of cancer will then be solved.

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Ectopic pregnancy in Shiraz, Iran

Study of 10 year records (154 cases)

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THIS is an attempt to report all patients with ectopic pregnancies who came to operation in the city of Shiraz, Iran, over a period of 10 years. A search was made among all of the various hospital records and those of the surgeons who have operating facilities in their offices. The most objective records were found in the Christian Mission Hospital which was established 30 years ago and has obtained extensive patronage of the Iranian citizens of this region. For 10 years it has been under the control of one of us (J. C.) who has diagnosed, operated upon, and written the histories of 97 of the 154 patients. Three other patients here were subjected to laparotomy but no ectopic pregnancy was found. These cases extend over a period of 10 years but the records of 1951, possibly amounting to 8 or 9 cases, were lost. Twenty-one cases were collected from the Saadi Hospital. This is the teaching hospital in connection with the Shiraz Medical School. These records are obtained mainly from abstracts, inasmuch as the original records up to 3 years ago have been destroyed. These patients all were under the care of one of us (M. S.) who in private practice had 15 other cases. Thirteen cases were from the private practice of Dr. Hassan Ali Fatehnejad. Eight cases were from the

records of Nemazee Hospital which was established 5 years ago. The total number of cases was 154.

Population from which the patients came

The figures on the population and numbers of pregnancies were obtained personally from Abol Hasan Hekmat, Chief of the Statistics Office of Shiraz, and are based in part on the national census of 1956: population of Shiraz, 170,759; population of outlying districts with radius of 60 kilometers, 230,699; total, 401,458.

There is an unexplained discrepancy in these figures. The birth rate is apparently much higher than the 1956 figure of 2.9 per cent for all of Iran.

Of this vast number of pregnancies, 10 years ago less than 1,000 patients annually were delivered in a hospital or maternity shelter. At the present time approximately 2,500 are hospitalized and 1,500 of these are at the Red Lion and Sun Hospital where they are quite efficiently delivered by trained midwives under the supervision of the obstetricians of the Medical School.

The question arises, "How many die without medical attention?" as it is recognized that women in this part of the world are loathe to be attended by a male physician. A cursory search of mortality records revealed no inordinate number of deaths among women of childbearing age. Further-

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Saadi Hospital.*

more, the medical system in use in Iran is one of *Behdars* in the villages. These are medical students who have finished 4 years of medical school instruction. They then practice without internship for a stated number of years in the outlying districts including usually a village of 5,000 to 20,000 people. While they may be the only physicians for from 10,000 to 40,000 individuals, and without hospitals, they are attended by midwives who tend to prenatal care and do the actual deliveries in the homes. After his time of such service the physician may return to the medical school for further instruction, internship, and often postgraduate work in foreign countries. There are quite a number of these in the upper class at the Shiraz Medical School at the present time.

Questioning of those who have served as *Behdars* for up to 5 years has not revealed a serious problem with ectopic pregnancy since most of the women with this condition are sent to the nearest hospital center for treatment. Many deny that they have ever seen or heard of an ectopic pregnancy in their district although, on questioning, they seem to know the signs and symptoms quite well. Unrealistic as it may seem, it appears that not more than one pregnancy in a

thousand here is ectopic. (This is based upon records of the past 5 years only.) A simultaneous study of hydatidiform mole was made upon the same group of patients and 119 cases were collected. It is realized that hydatidiform mole is far less painful and may terminate suddenly and spontaneously and consequently is much less likely to be seen in a hospital. However, one may conclude that the ectopic pregnancy rate here is low while that of hydatidiform mole is much higher than in the United States, and it may actually approach the high rate of the Orient.

The ages of the patients ranged from 15 years, of which there were 3, to 45 years, of which there were 2. Table II lists the ages per half decade in comparison with those of the patients with hydatidiform mole.

The median age for ectopic pregnancy was 28 years and for hydatidiform mole in the same group was 26 years. It may possibly be that the older patients more likely remained at home and had spontaneous abortions.

The exact age of each patient was not accurately known since beginning with age 25 they tended to be somewhat grouped at 25, 30, 35, and 40.

In respect to the four cardinal signs or symptoms of ectopic pregnancy stressed by Heaney,^{1,2} amenorrhea was mentioned in the history in 124 instances as follows: none in 9 cases; duration of one month or less, 49 cases; 2 months, 38 cases; 3 months, 18 cases; 4 months, 7 cases; 5 months, 1 case; and 6 months, 2 cases.

Vaginal bleeding was noted in 81 cases; no vaginal bleeding in 23 cases and no note in the remainder.

The symptom of pain was recorded as lower abdominal in 76 cases, right lower quadrant in 25, left lower quadrant in 22, shoulder pain in 3, and no pain in 3.

Abdominal mass quite universally tender was reported as follows: right adnexal region, 34 cases; left adnexal region, 36; and merely lower abdominal, 20. Without a mass being noted, there was extreme tenderness in the cul-de-sac of Douglas in 5

Table I. Tabulation on the live births

Year		Shiraz	Outside with radius of 60 kilometer	Total
Christian	Moslem			
1957	1336	6,117	10,938	17,125
1958	1337	6,649	12,151	18,800
1959	1338	7,312	10,683	17,995

Table II

Age (years)	Ectopic pregnancy	Hydatidiform mole
10-14	0	1 (14 years)
15-19	11	12
20-24	23	26
25-29	46	41
30-34	42	27
35-39	24	9
40-44	6	3
45-49	2	0

other cases; in the right side 2, and in the left side 2. In the remainder the record was incomplete.

Surgical shock was estimated upon the following evidence: (1) a record of shock, (2) upward of 1,000 c.c. of blood in the abdominal cavity at operation, or (3) blood pressure less than 100 systolic, and rapid pulse rate.

According to this there was surgical shock in 52 cases, about one third of the series, and probably in others operated upon without much record.

Laboratory data were seldom recorded. The hemoglobin level was noted as 7 Gm. in 2 cases; 8 Gm. in 7 cases; 9 Gm. in 7 cases; 10 Gm. in 10 cases; 11 Gm. in 22 cases; 12 Gm. in 5 cases, and 13 Gm. in 3 cases. The leukocytes were noted to be less than 8,000 in 15 patients and between 8,000 and 17,000 in 18 patients.

The diagnosis on admission was ectopic pregnancy in 91 cases, suspected ectopic pregnancy in 10 cases, doubtful in 16 cases, endometriosis in 1 case, twisted ovarian cyst in 1 case, intrauterine pregnancy in 1 case, and appendicitis in 1 case. One case with diagnosis of parovarian cyst proved at operation to be tubal pregnancy eroding into the broad ligament with resulting hematoma. In the others no record was made and many of these were emergency cases where operation was probably for ectopic pregnancy.

In respect to therapy, there was no operative delay in 80 cases, 1 day in 22, 2 days in 10, 3 days in 4, 4 days in 2, 5 days in 2, 6 days in 5, 7 days in 6, and 8 days in 2 cases. The remainder had inadequate records. There were noted 4 exploratory laparotomies. Rarely posterior colpotomy or needle puncture was used in diagnosis.

Pathology. Right ampullar pregnancy was noted in 75 cases; left ampullar 65 cases; bilateral 2 cases; isthmic 5 cases with 3 on the left side; fimbria 2 cases both on the right side; cornual 1 on the right; broad ligament hematoma 1 on the left. One patient had in addition an early intrauterine twin pregnancy. Several patients were reported to have passed decidual casts. In 3

cases there was no exact record of the site. Free blood in the abdominal cavity at operation was recorded: none 3 times; 1-plus 21 times; 2-plus 2 times; 3-plus 18 times; 4-plus 13 times. The remainder were doubtful or there was no record.

Evidence of infection. There was history of previous tubal insufflation in 1 patient, previous dilatation and curettage in 9 patients, old appendicitis in 1 patient, old pelvic adhesions in 8 patients, severe cervicitis in 5 patients; history of tuberculosis in 1 patient, and old salpingitis in 1 patient. The Kahn test was reported positive in 3 patients.

Transfusions were used sparingly in comparison with hospitals in the United States. Frequently only one transfusion was administered, rarely 2 or 3. Thirty-three patients were recorded as having received blood transfusions. In addition one of us (J. C.) made use of "autotransfusion" in 11 patients and with good results.

Heterotopic pregnancy

H., aged 23, Kahn test slightly positive, entered the Christian Mission Hospital in mild shock with a history of sudden abdominal pain of one day's duration. There was vaginal bleeding and the fundus was very tender on motion. The hemoglobin level was 62 per cent with 2.32 million erythrocytes. Immediate laparotomy revealed a right ampullar ectopic pregnancy and a pregnant fundus, which aborted twins 6 days later. The age of the pregnancy was not stated.

Mortality

In the entire series only one death was recorded and the convalescence in the others seemed to proceed normally.

Z., aged 30, mother of 5 children with 4 living, presented with a history of amenorrhea for 3 months and recent attacks of abdominal pain and syncope. She had had five such attacks in the previous month. She had typical signs and symptoms of ectopic pregnancy, immediate diagnosis, and no delay in operation. There was a moderate amount of blood in the abdominal cavity and a 4 months' fetus in a sac associated with the right tube. There was no record of a transfusion and she died on the second post-operative day.

Summary

Review has been made of all cases of ectopic pregnancy (154) which came to operation, less possibly 10 per cent, in all of the surgical facilities of the city of Shiraz, Iran. These are the only operating facilities for a population of approximately four or five hundred thousand persons within 60 kilometers.

The usual signs and symptoms where available from the often meager histories are listed. One third or more of the patients were emergencies at the time of admission.

The pathologic findings are listed, including 2 cases of bilateral ectopic pregnancy

and one case of heterotopic pregnancy with twins in the uterus.

There was one death presented in as much detail as possible from the recorded history.

From this conscientious study it was concluded that the incidence of ectopic pregnancy in this region is low, and indicates that for every 4 ectopic pregnancies there are 3 hydatidiform moles.

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*Bangham, D. R., Hobbs, K. R., and Tee, D. E. H.: Transmission of Serum Proteins From Fetus to Mother in the Rhesus Monkey, p. 1173.

Bangham, Hobbs, and Tee: Transmission of Serum Proteins from Fetus to Mother in Rhesus Monkey, p. 1173.

In this preliminary report fetal rhesus serum containing protein labeled with I^{131} was administered to each of 3 fetuses in utero as follows: in A after a midline incision exposed the fetus the dose was injected into a placental vein; in B into the fetal peritoneum; in C a cannula was inserted into the fetal peritoneal cavity and after 6 days allowed for repair the dose was injected through the cannula. Samples of blood and liquor were taken from each monkey at 1 and 4 hours and at longer intervals after the injections. Monkey B aborted after 24 hours; no fetal movements were felt in Monkey A after 48 hours; Monkey C gave birth to a normal baby 7 weeks after operation. In all the maternal sera, radioactivity was found in the albumin fraction 18 hours after injection and increased in concentration in samples taken up to 8 days. Radioactivity in the gamma globulin fraction isolated by electrophoresis and by chromatography appeared at 24 hours and also increased in concentration. Little radioactivity occurred in the electrophoretic fractions between albumin and gamma globulin. Thus the maternal samples were quite different from the dose material, the serum obtained from the fetus that aborted 24 hours after the operation, and the serum taken from an adult and from a 1-month-old

baby up to 8 days after being given a similar dose of I^{131} -labeled fetal serum.

Thus albumin and gamma globulin can return to the mother from the fetus in a selective fashion inasmuch as little radioactivity was found in the maternal alpha and beta globulins. Negligible amounts of radioactivity were found in the liquor amnii. Previous experiments (Bangham, D. R.: *J. Physiol.* 150: 250, 1960; Bangham, D. R., Hobbs, K. R., Terry, R. J.: *Lancet* 2: 351, 1958) have shown that I^{131} -labeled albumin and gamma globulin can be transferred from the mother to the fetus without the liquor amnii playing a significant part. Albumin in the liquor exchanges rapidly with the mother's intravascular serum albumin. The present experiments show that little of the serum proteins which occur in the liquor in midpregnancy can be derived from the fetus.

David M. Kydd

Dec. 3, 1960.

*Russell, J. K.: Artificial Insemination (Husband) in the Management of Childlessness, p. 1223.

Russell: Artificial Insemination (Husband) in Management of Childlessness, p. 1223.

In this report the results of 55 trials of artificial insemination with the husband's semen are detailed. Each course consisted of 3 inseminations on the twelfth, fifteenth, and eighteenth days of the cycle and extended over several months (shortest, 2 months; longest, 2 years intermittently). At first the semen was injected into the cervical canal but because of infection and unpleasant symptoms intracervical insemination was discontinued and thereafter the fresh semen was sprayed around the cervical os. Of 34 women whose husbands had oligospermia (below 10 mil-

*These articles have been abstracted.

lion per milliliter) 2 conceived during treatment. However, 8 of these patients conceived subsequently without insemination. Thus, oligospermia is not considered to be an indication for insemination. In 8 instances of apparent cervical hostility 1 patient conceived during treatment but 2 others became pregnant after the insemination had been discontinued. Thus, the procedure does not seem to increase the likelihood of conception.

Artificial insemination was carried out in 7 women whose husbands were impotent and 6 of these women conceived. Two women whose husbands had hypospadias both conceived and 2 patients who had negative postcoital tests both conceived after the procedure. These, then, would appear to be the principal indications for insemination. Impotence can take less obvious forms and ineffective ejaculation may be more common than is generally suspected. In such instances insemination may be helpful whereas when the quality of the semen is poor there is no evidence that the procedure improves the chance of conception.

David M. Kydd

Dec. 10, 1960.

*Shrand, H., and Ruthven, C. R. J.: Effect of Triiodothyronine on Serum-Bilirubin Level and Neonatal Development of the Premature Infant, p. 1274.

Shrand and Ruthven: Effect of Triiodothyronine on Serum-Bilirubin Level and Neonatal Development of Premature Infant, p. 1274.

Excluding infants with Rh and ABO incompatibility, 28 premature infants weighing between 900 and 2,400 grams at birth were allocated at random to a control group and to a group each member of which received 10 μ g of triiodothyronine orally in a single daily dose. The concentration of bilirubin in the serum was determined on the first day of life and then daily until the peak values were passed. In the control group of 14 infants the mean peak bilirubin level was 8.95 ± 1.33 mg. per 100 ml. which was reached in 97 ± 10.9 hours after birth. In the group of 14 treated infants the mean peak bilirubin level was 11.5 ± 1.31 mg. per 100 ml. which was reached in 105 ± 11.6 hours after birth. These differences were not considered to be of significance so that the effect of triiodothyronine that was reported previously (Lees, M. H., and Ruthven, C. R.: *Lancet* 2: 371, 1959) was not found in this series. Although the mean

weight lost by the controls was less than the treated, the difference was not significant and in both groups the weight was regained within the same time. No differences were observed between the members of the two groups so far as temperature regulation, feeding ability, degree of alertness, lethargy, or general appearance was concerned.

Although Westphal and associates (A. M. A. J. *Dis Child.* 98: 138, 1959) reported statistically significant increase in the number of treated infants whose serum bilirubin levels either fell or remained the same between the second and fourth days of life when compared with the untreated control infants, they employed larger doses (25 μ g triiodothyronine) and the series was in other ways not strictly comparable.

David M. Kydd

Dec. 31, 1960.

*Duncan, S. L. B., Lawrie, J. H., and MacLennan, H. R.: Bromelain and the Cervix Uteri, p. 1421.

Duncan, Lawrie, and MacLennan: Bromelain and the Cervix Uteri, p. 1421.

Because bromelain (a mixture of enzymes prepared from the stems of pineapple plants) has been reported to be of value in the treatment of dysmenorrhea, studies of the action of this mixture were undertaken. Bromelain dissolved in 50 ml. of water was instilled into the vaginas of each of 5 women whose cervixes appeared to be normal but who were about to undergo hysterectomy because of functional uterine bleeding. At varying periods of time (from 20 minutes to 12 hours after the instillation) the uterus was removed and the cervixes were examined histologically. In a fifth woman one half of the cervix was removed by vaginal hysterectomy, the material was instilled, and the remaining cervix was removed 20 minutes later. No histological changes of any kind were found in any of the sections studied regardless of the period of treatment with bromelain. Specimens of cervix were exposed to the mixture *in vitro*. No histological change was noted after 12 and 24 hours of exposure but after 48 hours the outline of the cell membrane was lost and there was discrete fiber formation. These results indicated that there was no proteolytic effect *in vivo*. Specimens of mucus obtained from the cervical canal and from the intracervical glands were mixed with a solution of bromelain. There was no immediate effect, 48 hours being required for liquefaction. Tenacious

mucus from nabothian follicles required 3 to 4 days for liquefaction.

Three further specimens of apparently normal uterus and cervix immediately after hysterectomies were performed on patients who were premenopausal were studied. Strips of these tissues were treated with oxytocin (Pitocin) before and after the addition of bromelain to the saline bath in which they were suspended. Although bromelain caused no immediate effect either on the spontaneously contracting tissue or on oxytocin-induced contractions in 6 of 7 tissues, a slow inhibition of contractions starting after 20 minutes was observed. Furthermore, a uterine horn of a rat contracted rhythmically, responded by a spasmodic contraction to the addition of oxytocin, and was inhibited by the addition of bromelain. The conclusion is reached that no evidence of proteolytic or mucolytic activity of the mixture was found but oxytocin-induced spasm of cervical muscle is reduced and bromelain may therefore have an antispasmodic action. No explanation for the claim that dysmenorrhea is relieved in later cycles by a single application was found. *David M. Kydd*

Vol. 1, Jan. 7, 1961.

*Morgan, E. H.: Plasma-Iron and Hemoglobin Levels in Pregnancy, p. 9.

Morgan: Plasma-Iron and Hemoglobin Levels in Pregnancy, p. 9.

All patients attending two different antenatal clinics at the King Edward Memorial Hospital for Women, Subiaco, Western Australia, were studied during a period of 6 months. Those attending one clinic (234 patients) received no treatment while those attending the other (122 women) were asked to take 100 mg. Fe^{++} per day in the form of ferrous gluconate. The concentrations of hemoglobin and plasma iron, the mean corpuscular hemoglobin concentration (MCHC) and the plasma total iron-binding capacity (TIBC) were determined when the patient was admitted to the clinic and at one or two other visits during the pregnancy. Mean values were then calculated for each 3 weeks of pregnancy. In the control group the mean hemoglobin concentration fell from 13.5 Gm. (13.1 to 14.1) per 100 ml. at the fifth week to a minimum value of 12.4 Gm. (10.7 to 14.9) per 100 ml. at about the thirtieth week and then rose to a mean value of 12.7 Gm. (10.8 to 14.6) at the fortieth week. No patient developed a hemoglobin concentration of less than 10 Gm. per 100

ml., which probably indicates that the iron status of Australian women is generally good. MCHC did not change appreciably (32.8 at both the fifth and fortieth week). The plasma iron fell from 123 μg (74 to 161) per 100 ml. to 93 μg (92 to 186) per 100 ml. and TIBC rose from 332 μg (242 to 396) at the fifth week to 569 μg (386 to 712) at the fortieth week. Although a correlation between the concentrations of hemoglobin and plasma iron was found, no correlation between hemoglobin concentration and TIBC was observed.

In the patients who received iron, the concentration of hemoglobin also fell, reaching a minimum value of 12.5 Gm. (10.9 to 14.3) per 100 ml. at the twenty-eighth week but then rose to a somewhat higher level than in the control group at the fortieth week (13.5 Gm. [11.4 to 15.3] per 100 ml.). MCHC in the treated patients was always slightly higher than in the control patients. No significant difference in the concentration of plasma iron developed in the treated patients except that in the last month of pregnancy a rise in the concentration appeared that did not occur in the control patients. Although TIBC rose progressively in the treated patients, the rise began some 3 months later than in the control patients (i.e., at the sixth rather than at the fifth month). Also, the rise was less marked in treated patients (from 350 [310 to 408] at the seventeenth week to 464 μg [352 to 605] per 100 ml. at the fortieth week).

In these Australian women, therefore, the need for supplementary iron appeared to be not large. Nevertheless, women who received additional iron had a somewhat higher concentration of hemoglobin and MCHC at term than those who did not, and the plasma iron concentration during the last month was higher. Supplementary iron also diminished the rise in TIBC that has been observed in pregnancy. A correlation was found between the length of time that iron is given and the lessened height to which values of TIBC rise, suggesting that iron to be maximally effective should be given early in and throughout pregnancy. However, the administration of iron does not abolish the rise of TIBC and the mechanism of this rise remains obscure.

David M. Kydd

Jan. 14, 1961.

*Ohno, Sussumu, and Makino, Sajiro: The Single-X Nature of Sex Chromatin in Man, p. 78.

*Stewart, J. S. S., and Sanderson, A. R.: Sex-Chromatin Body in Normal Human Testis, p. 79.

Ohno and Makino: Single-X Nature of Sex Chromatin in Man, p. 78.

Previous studies of germ and somatic cells of both sexes of rats have indicated that only one X chromosome in the female somatic cell shows precocious condensation and that the sex-chromatin body represents a single X rather than a fused heterochromatic region of two X's. In this report cells from the liver of 2 fetuses at about the fourth month of gestation were studied. In the male among several small chromocenters always present one seemed more distinct than the others but male nuclei were always void of a chromocenter approaching the size of the sex chromatin seen in female cells. In the female at prophase only one chromosome in each nucleus was heavily condensed along its entire length. This element which was much larger than seen in the male nuclei apparently represented a large chromosome and corresponded roughly in size to the sex chromatin seen during interphase and to the submediocentric chromosome belonging to the 6-12 group of female metaphase. The conclusion was that sex chromatin of man, as in the rat, represents a single X chromosome. Previous reports that both XXX females and XXXY males have two sex-chromatin bodies in many nuclei support the belief that only one X chromosome is required rather than a fusion of two X's. Why one of the two X's in female somatic cells persistently forms a sex-chromatin body remains unknown. The suggestion that the X chromosome involved is of paternal origin has been confounded by the finding of Ohno, Kaplan, and Kinoshita (Proc. Am. A. Cancer Res. 3: 139, 1960) that X^oO female mice failed to display precocious condensation. Also the suggestion that one set of autosomes will suppress heteropyknosis in one X (e.g., an XXX cell has one set of autosomes, one suppressor, and so two heteropyknotic X's) has been made unlikely by the report of an instance of chromatin-positive Turner's syndrome that is XO.

David M. Kydd

Stewart and Sanderson: Sex-Chromatin Body in Normal Human Testis, p. 79.

In 7 subjects from whom testicular tissue was obtained for a variety of reasons by biopsy or by operation the nuclear sex by conventional methods was chromatin negative. In three of the

testicular preparations suitable plates were obtained. The chromosome number (46) and sex chromosome constitution (XY) were confirmed from primary spermatocyte metaphases or from spermatogonial metaphases. Despite this normal male karyotype sex chromatin was present in 10 per cent of the germ-cell nuclei. The sex-chromatin body was present in all nuclei of different sizes, apparently in spermatogonia and in primary and secondary spermatocytes. It was most prominent in primary spermatocyte nuclei during the early prophase and in these instances appeared to be connected to the nucleolus by a fine chromatin thread. During the later stages of early prophase the sex-chromatin body became larger and vesicular. In late prophase a heteropyknotic condensation, apparently the X or XY chromosome complex, was present.

These observations appear to support the view previously reported (Stewart, J. S. S.: Lancet 1: 825, 1960) that the sex-chromatin body is derived from the heterochromatin portion of a single X chromosome. Sex chromatin may also be detectable in normal males during mitotic prophase in cells other than spermatogonia. Further support for the hypothesis that the maximum number of sex-chromatin bodies in somatic nuclei during interphase is one less than the number of X chromosomes comes from a study of the frequency of sex chromatin in somatic cell nuclei. The following formula was used to predict, in subjects with abnormal karyotypes, the frequency of nuclei with one or more sex-chromatin bodies: $1 = [nP + (1-n)]^{x-1}$ where n is the proportion of nuclei which are chromatin positive (P), $(1-n)$ is the proportion of chromatin negative, and X is the number of X chromosomes.

David M. Kydd

Jan. 21, 1961.

*Field-Richards, S., and Snaith, L.: Allylestrenol: A New Oral Progestogen, p. 135.

Field-Richards and Snaith: Allylestrenol: A New Oral Progestogen, p. 135.

Allylestrenol, a synthetic derivative of 19-nor-androstenedione, was given to 50 patients for periods varying from 3 to 6 months. Of 13 patients with premenstrual tension who were given 5 to 10 mg. of the drug daily for 3 to 6 days in each menstrual cycle, 8 were greatly improved, 2 were improved but with increased libido, 1 was moderately improved, 2 were unimproved and complained of some low pelvic pain during treat-

ment. In 6 instances of recurrent abortion each taking place between the sixth and tenth week of pregnancy, 15 mg. allylestrenol was given daily from the sixteenth to the twenty-sixth day of the cycle for 3 months. One conceived in the first cycle, 3 in the second, and 1 in the third. The remaining patient showed full secretory endometrium but failed to conceive. The 5 who conceived were given a further course of 10 mg. daily for 16 weeks. Three pregnancies continued to term, one continued to term despite several small hemorrhages during the early weeks and one pregnancy was ended by an abortion at the twelfth week. One instance of threatened abortion in a patient who previously had had a normal pregnancy was treated with 15 mg. allylestrenol daily from the tenth week for 10 days. Bleeding continued and curettage was required eventually. Seven patients with suspected failure of nidation in whom the endometrium had shown poor secretory activity and whose temperature charts had low biphasic readings were given 15 mg. of allylestrenol daily from the sixteenth to the twenty-sixth day of each cycle for 2 months. Biopsy specimens in the immediate premenstrual phase showed secretory activity. Five patients became pregnant within 3 or 4 months after biopsy although one of these aborted at the eighth week. Despite treatment for 8 months, 2 patients did not conceive.

Two patients, each of whom had had one previous child but who had secondary amenorrhea, were each given 10 mg. allylestrenol daily for 20 days in successive cycles without estrogen priming. Neither patient had any menstrual loss.

Six patients with menorrhagia thought to be due only to hormonal imbalance had been treated with hormones or by curettage during the previous 18 months with temporary or little relief. Three had received testosterone with valuable results in 2 although testosterone was discontinued in all because of side effects. Five of these patients were each given 15 mg. allylestrenol daily from the twelfth to the twenty-sixth day. In 3 the results were satisfactory in that the period of bleeding was reduced and the loss, although it remained heavy, became less with each successive cycle. Two patients failed to respond. The sixth patient received 15 mg. of allylestrenol from the fifth to the twenty-fifth day but she had such severe hemorrhage that hysterectomy was performed after one cycle.

Four patients had metropathia, all of whom had had a curettage without any abnormal pelvic pathological changes being found and in whom endometrial biopsies showed the typical pattern of irregular epithelial shedding. After receiving 15 mg. allylestrenol daily from the twelfth to the twenty-sixth day of the cycle for 3 cycles, 3 of these patients were found to have secretory endometria. Two patients improved but their endometria were described as poor secretory in character. One patient became pregnant. Six other patients whose menstrual losses were clearly anovular were given estrogens followed by allylestrenol. In all, secretory endometrium and satisfactory luteal phases were produced.

Two patients with endometriosis were treated but the results were unsatisfactory. Four patients with primary dysmenorrhea were treated with 10 mg. of allylestrenol daily for about 3 weeks of the cycle. In 2 of these patients the response was excellent. In the other 2 there was slight improvement but the drug had to be discontinued because of increased libido.

Allylestrenol, therefore, although not the most potent of the synthetic orally active progestogens was very well tolerated and gave results expected of a progestogen. The increased libido induced in 2 patients with dysmenorrhea was unexpected inasmuch as pharmacological examination found the drug to be not androgenic. Further investigation is required.

David M. Kydd

Wiener klinische Wochenschrift

Vol. 71, May 8, 1959.

*Szendi, B., and Lakatos, I.: Diabetes Insipidus in Pregnancy, p. 338.

Szendi and Lakatos: Diabetes Insipidus in Pregnancy, p. 338.

Clinical data are presented from a 21-year-old primigravid dwarf with the combination of diabetes insipidus and pregnancy. Vaginal delivery of a 2,700 gram infant was possible. Details of the management of the patient are given, and an extensive analysis of the pertinent literature is presented. The authors conclude that diabetes insipidus is an isolated disturbance of the diencephalic-hypophyseal system and that the remaining hormonal functions of this system, including its oxytocic function, are not altered by diabetes insipidus.

Douglas M. Haynes

Aug. 7, 1959.

*Engelhard, E.: On Anterior Hypophyseal Insufficiency Following Severe Postpartum Hemorrhage, p. 570.

Engelhard: Anterior Hypophyseal Insufficiency After Postpartum Hemorrhage, p. 570.

The pathologic anatomy and the clinical manifestations of anterior pituitary insufficiency following episodes of obstetric hemorrhage are described. It is especially emphasized that anterior pituitary insufficiency is only rarely diagnosed, and atypical forms often remain unrecognized because of their uncharacteristic clinical symptoms. The importance of an adequate history and the significance of severe and long-lasting secondary amenorrhea following pregnancy are emphasized. A case of Sheehan's disease after a severe postpartum hemorrhage is reported, and various methods of substitution therapy are discussed, including treatment with follicular hormone, testosterone, small doses of thyroid extracts, cortisone, and ACTH. In the author's experience, low-grade irradiation of the hypophysis has some usefulness. *Douglas M. Haynes*

Oct. 16, 1959.

*Bandhauer, K., and Marberger, H.: A Case of Endometriosis of the Ureter, p. 806.

Bandhauer and Marberger: Endometriosis of the Ureter, p. 806.

The authors report a case of ureteral stenosis with secondary hydronephrotic atrophy treated by nephrectomy in which the etiology of the stenosis was demonstrated in the pathologic specimen to be primary external endometriosis of the ureter. In contradistinction to endometriosis involving the urinary bladder, the incidence of primary endometriosis of the ureter is extremely small, as is endometriotic involvement of the kidneys (the authors found 4 cases in the literature). The patient was 41 years old, and after surgical extirpation there was no necessity for hormonal or other supportive treatment. No other foci of extrauterine endometriosis were encountered. *Douglas M. Haynes*

Vol. 72, April 15, 1960.

*Grünberger, V., and Senker, F.: On the Question of Indications for Cesarean Section, p. 271.

Grünberger and Senker: Indications for Cesarean Section, p. 271.

The authors review statistics from German publications to demonstrate decreasing mortality as-

sociated with cesarean section, using the data as justification for widening of the indications. A comparison is made between the indications for cesarean section at the First Women's Clinic of the University of Vienna for the period 1936 to 1940 on the one hand, and 1954 to 1958 on the other. As a result of widening of the indication, the cesarean section rate rose from 0.96 to 2.45 per cent. The most common indication was contracted pelvis, but this decreased in relative frequency from 72.8 per cent in the first period studied to 17.7 per cent in the second period; 13.8 per cent of the sections were performed for placenta previa in the second period as compared with 8.7 per cent in the earlier time. In the light of the data presented, the authors suggest that certain clinical features may indicate cesarean section, even though this may not have formerly been the case. These factors include the combination of prolonged labor in an elderly primigravida; breech in an elderly primigravida; breech presentation and prolonged labor; failed induction, and some selected cases of apparent fetal distress. These and other widened indications for cesarean section may have helped to bring about the decreased maternal mortality (from 6.8 to 0.6 per cent) and the decreased fetal mortality (from 4.3 to 3 per cent) observed during the second period of study.

Douglas M. Haynes

April 22, 1960.

*Kremer, H., and Narik, G.: Indications and Results of the Manchester Operation, p. 284.

Kremer and Narik: Indications and Results of the Manchester Operation, p. 284.

The authors report the results in 186 patients subjected to the Manchester operation, 151 of whom were adequately followed up. In the latter group, 80.13 per cent reported complete success, 13.91 per cent showed marked improvement, and 5.9 per cent had unsatisfactory results. The authors express the opinion that the Manchester operation seems to them to be the best currently used conservative vaginal operation for uterine prolapse.

Douglas M. Haynes

Wiener medizinische Wochenschrift

Vol. 109, June 27, 1959.

*Halter, G.: Contribution to the Study of the Acute Abdomen During the Puerperium, p. 540.

Halter: Contribution to the Study of the Acute Abdomen During the Puerperium, p. 540.

The author reports the case history of a patient who developed an acute abdomen during the puerperium which proved to be caused by a thrombosed infundibulopelvic ligament. The statistical data available from the literature on puerperal thromboses are reviewed, and contemporary methods of treatment are summarized.

Douglas M. Haynes

Sept. 26, 1959.

*Huber, A.: Genital Tuberculosis in Ethiopian Women, p. 729.

Huber: Genital Tuberculosis in Ethiopian Women, p. 729.

In 1,000 endometrial biopsies taken from Ethiopian women during a 4 year period, 35 cases of tuberculous endometritis were encountered, a startlingly high incidence of 3.5 per cent. These patients had usually presented themselves because of infertility. The author presents detailed data on all types of genital tuberculosis, with special reference to the unfavorable living conditions in Ethiopia associated with this unusually high frequency of female genital tuberculosis.

Douglas M. Haynes

Vol. 110, May 28, 1960.

*Nagyiványi, R.: Prophylaxis Against Permanent Damage Following Pregnancy Toxemia, p. 446.

Nagyiványi: Prophylaxis Against Permanent Damage Following Pregnancy Toxemia, p. 446.

The author was able to follow 86 of 170 women treated for toxemia of pregnancy. This postpartum follow-up examination was carried out from 2½ to 3 years after delivery. The examination consisted of a physical examination, urinalysis, and mensuration of the blood pressure. If the urine was positive for albumin or the blood pressure greater than 140/90, a renal concentration test was performed, the eye grounds were examined and the creatinine clearance was determined. Posttoxemic hypertension was found in 18 patients; the average blood pressure was 160/100. Eight women demonstrated the signs of chronic nephritis. Four of these showed alterations in concentrating ability and creatinine clearance. Twenty-six of the 86 patients (30.2 per cent) therefore showed permanent damage, with posttoxemic hypertension in 20.9 per cent

and chronic nephritis in 9.3 per cent. In 8 of the hypertensive women, there was a family history of high blood pressure. Six of the patients were markedly obese, but none of them was diabetic. Seventy per cent of the women demonstrating ostensible permanent damage were 30 years of age or older. The duration of the toxemia varied between 2 weeks and 4 months. The author believes that permanent damage following toxemia depends on the intensity of the symptoms, the duration of the toxemia, heredofamilial tendency to hypertension, obesity, nephritis, and failure to treat the toxemia promptly following the earliest possible diagnosis. His data indicate that the concept of permanent posttoxemic damage is a real one.

Douglas M. Haynes

June 11, 1960.

*Navratil, E.: Contribution to the Question of the Local Rate of Growth of Invasive Squamous Carcinoma of the Portio, p. 494.

Navratil: Contribution to the Question of the Local Rate of Growth of Invasive Squamous Carcinoma of the Portio, p. 494.

Navratil reports the case of a patient who demonstrated a particularly slow local growth rate of carcinoma of the cervix; 7 years and 4 months following histologic diagnosis of an early invasive carcinoma, the patient's lesion represented only a Stage IIa. The author points out that the rate of growth of the tumor depends both on the rate of proliferation of the tumor cells and on the reaction of the surrounding tissues. The illustrative case shows that in exceptional instances the ordinarily rapid spreading cervical carcinoma may metastasize very slowly.

Douglas M. Haynes

June 25, 1960.

*Bergmann, H.: On the Question of Interruption of Pregnancy in Rh-Immunized Women, p. 507.

Bergmann: Interruption of Pregnancy in Rh-Immunized Women, p. 507.

The author reports 2 cases of women demonstrated to be carriers of Rh-immune bodies in whom in apparently hopeless situations following repeated stillbirth and abortion a healthy Rh-negative infant was born. Criteria are set down to estimate the fundamental degree of hopelessness in pregnancy associated with demonstrable

Rh immunization. The author stresses the importance of the history, the homo- or heterozygosity of the father, and investigation of antibody titers during pregnancy. The probable genotype of the father may occasionally be in error, so that from time to time a favorable outcome may be expected in apparently hopeless situations. There will continue to be such occasional cases until an absolutely certain determination of the actual genotype will be possible in all cases. This will not be so until an anti-d serum has been developed. Since present methods are not sufficient to prognosticate accurately the outcome of a pregnancy, the author objects to interruption of pregnancy because of possible hemolytic disease of the newborn, even though an occasional exception might be justified.

Douglas M. Haynes

July 2, 1960.

*Meixner, H.: Fatal Pulmonary Embolism in Gynecology and Obstetrics, p. 26.

*Huber, A.: Uterine Carcinoma and Circumcision—Investigations in Ethiopia, p. 571.

Meixner: Fatal Pulmonary Embolism in Gynecology and Obstetrics, p. 26.

The author reports on observations on the incidence and treatment of pulmonary embolism during the 14 years from 1945 to 1958 in the Gynecologic Clinic of Innsbruck University. This period is divided into two segments of 7 years each. During the first 7 years, anticoagulant therapy was not used in either prophylaxis or management of pulmonary embolism of thromboembolic disease, whereas in the second period of 7 years anticoagulant therapy was routinely employed. During the 14 years covered, there were 19 instances of fatal pulmonary embolism when the statistics for both the gynecologic and obstetric division were amalgamated. Since the total number of patients involved was 43,575, the over-all incidence of fatal pulmonary embolism was 0.043 per cent. Fourteen of the fatal instances of pulmonary embolism occurred on the gynecologic service and 5 on the obstetric service. In the first 7 year period when anticoagulants were not used, 5 of the fatal cases were gynecologic and 4 obstetric, whereas in the second observation period, 10 fatal pulmonary emboli occurred in all, 9 of which were in gynecologic patients and only one in an obstetric

patient. There was, therefore, an actual increase in the incidence of fatal pulmonary embolism in the gynecologic division in the second as compared with the first observation period, whereas in the obstetric patients, fatal pulmonary embolism decreased from 0.042 per cent in the first 7 year period to 0.0086 per cent in the second period. The single fatal instance of pulmonary embolism occurring in the 1952 to 1958 period followed a cesarean section in a patient who had had no anticoagulant therapy. Among the 14 cases of fatal pulmonary embolism in the entire 14 years on the gynecologic service, 10 were in postoperative patients and 4 followed spontaneous thrombosis. The 14 fatal cases in gynecologic patients represented 13.2 per cent of all deaths on the gynecologic service. Nevertheless, from the author's data, it appears that fatal pulmonary embolism in patients with clinical signs of thrombosis receiving anticoagulation therapy has become less common than it was before anticoagulation therapy was routine. Furthermore, the late sequelae of local thrombotic phenomena, such as chronic lymphedema of the legs, was reduced in incidence.

Douglas M. Haynes

Huber: Uterine Carcinoma and Circumcision, p. 571.

The author reports the incidence of uterine carcinoma in Ethiopia, including a large series from the Hospital of the Royal Guard and the official statistical analysis on the Ministry of Health of Ethiopia. The incidence of carcinoma of the cervix was approximately 50 per 100,000, a figure approximately parallel to that in West Europe or in the United States. The relationship of cervical to endometrial carcinoma was 25 to 1 in the author's personal series. Huber points out that if routine circumcision were of prophylactic value in the prevention of carcinoma of the cervix, as has often been claimed, one would expect to find a very low incidence of cervical carcinoma in Ethiopia because almost the entire male population of this country is subjected to ritual circumcision in earliest youth. This theory was not substantiated by the results reported here. Prophylactic circumcision seems to be of value only in the prevention of carcinoma of the penis.

Douglas M. Haynes

Correspondence

Occlusion of Fallopian tubes

To the Editors:

I would like to comment on the article entitled "Occlusion of the Fallopian Tubes With Tantalum Clips" by Drs. Neumann and Frick, which appeared on page 803 of the April, 1961, issue of the JOURNAL.

In 1957-1958 I, too, carried out experiments with the object of producing reversible sterility, despite the fact that in 107 cases where I had performed cornual resection of the Fallopian tubes I had never had a failure. These patients were observed for many years and no pregnancies had occurred. My reason for performing these experiments was to find a method which would be bloodless and which could be rapidly performed. The blood loss in some of my patients on whom I performed cesarean sections was at times considerable, and it took almost as much time to control the hemorrhage as it did to perform the section.

The experimental animals were rats, rabbits, and dogs. Only animals who were known to have had litters were employed. Tantalum clips and the cautery were used, but I will confine myself here to the results obtained with the tantalum clips.

The clips were placed as far lateral from the uterine cornua as possible. At this location the uterine horns roughly approximated the size of the human tube. In the paraffin sections both the uterine horns and the tubes were at times visible.

Seven dogs were operated on and it was possible to remate 4 of them after the application of the clips. Two of them conceived and bore live litters. One bitch who became pregnant and in whom Evans tantalum clips were employed was reoperated on after the pups were weaned, and it was found that the clips had shifted their positions and that the tubes were patent. The other dog who gave birth to a litter was also reoperated on and it was found that one of the clips had eroded into the lumen of the tube, and at this site a suppurative process was present.

None of the rabbits or rats conceived after

remating, but in a small percentage one or both tubes were found to be patent. Hydrosalpinx was a very frequent finding in the rabbits and rats and to a much lesser extent in the dogs.

Had the results in the tantalum clip technique been successful, it would have been ideal because of its lack of bleeding and the rapidity with which it could be performed. Unfortunately, in my experiments the method proved unreliable and in addition was at times complicated by the occurrence of hydrosalpinx and pyosalpinx.

A personal communication from a prominent surgeon informed me that he had personal knowledge of pregnancy occurring in 3 patients after the application of Evans tantalum clips.

Samuel S. Rosenfeld, M.D.

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April, 1961*

Reply by Dr. Neumann

To the Editors:

Dr. Rosenfeld's letter presents interesting experimental material that does not conflict with our experiences. I would like to add the following comments in regard to hydrosalpinx, pyosalpinx, and the reliability of the procedure:

1. After observing 16 tubes in monkeys we found a hydrosalpinx only once, when two separate clips had been applied to one tube.

2. There was no evidence of infections in the monkeys; bitches, however, seem to be more prone to pyogenic infections of the uterus and the tubes.

3. In regard to the effectiveness of the method, its target should be kept in mind; a 10 or 15 per cent rate of failure would be prohibitive in a medicolegally sophisticated environment. The same 85 per cent effectiveness might be rated relatively successful in regions of Pakistan or in the slums of Calcutta where efforts at promoting contraceptives have been stark failures. The potential of the procedure should be viewed not as an application of clips to the tubes to replace surgical ligations where indicated and feasible, nor even to replace the use of contraceptives in more knowledgeable and mo-

tivated populations, but in its combination with a speedy and inexpensive application through the cul-de-sac, if it should lend itself to large scale use.

Few American practitioners have been faced with this problem as it exists in some regions of Asia, and from their sheltered positions may lack realization of its magnitude. S. K. Dey, himself an Indian, described in *The Statesman* why the villager of West Bengali does not respond to family planning propaganda. "He suffers from a profound listlessness of spirit, is sunk into a state of utter hopelessness, in a perpetual twilight of the senses, which does not evoke normal reactions to ordinary stimuli. The biological urge is robbed of its human significance . . . , and reproduction becomes an animal function, a proliferation which leads as much to death as to life." Yet in such an environment roving teams of government physicians, performing cataract operations with astounding speed and skill, are accepted and work successfully. It might be possible to induce villagers to single visits, even where the repeated use of any contraceptive would be out of the question.

Stating the target of the procedure overshoots, of course, its present stage of development: it is merely to justify pursuing an approach to contraception which may not be infallible; experience and modifications of the staple design may greatly influence its reliability.

H. H. Neumann, M.D.

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May, 1961

Physiology of uterine isthmus

To the Editors:

I have read with interest the paper by Drs. Edward C. Mann, William D. McLarn, and David B. Hayt, which is published on page 209 of the February issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, and have also reviewed the prior study by Dr. Mann (*AM. J. OBST. & GYNEC.* 77: 706, 1959). Both papers deal with the physiology of the isthmus uteri as it is related to abortion. Employing new techniques in a very large number of patients, they have outlined an entirely new concept which summarily rejects both the prior concepts and the data upon which they are based. Possibly it was because of the very massive nature of their work that certain details have been omitted from

this presentation; but, without them, it is difficult for the uninitiated observer to make a binding appraisal either of the work itself or of its meaning. Among the data which would be helpful are the following:

1. How do the authors define "tone," "hypertonia," "hypotonia," and "atonia"? What relation do these definitions bear to the conditions of the experiments and to the findings?

2. What, exactly, is the volume of radiopaque solution which is introduced into the balloon? Is it the same in all cases? How does this compare with the normal, resting capacity of the nonpregnant uterine cavity? Is there a normal variation in capacity with the different stages of the menstrual cycle?

3. What is the range of pressures which were employed? For purposes of orientation and comparison, what is the normal intrauterine pressure at the height of a first or second stage labor contraction? In these experiments, at what pressure does the "secondary expansile unit" pop into the isthmic segment? Is this pressure the same for all patients in a particular stage of the menstrual cycle? Is it the same in the "hypotonia" cases as in the "hypertonia" ones? Exactly how many cases were studied in each menstrual phase? Of these, how many individual patients were studied repeatedly at different stages of the cycle to support the statement that "the normal isthmus is alternately hypotonic, hypertonic, and atonic" depending on the phase of the menstrual cycle? What was the range of pressures achieved in each, and is there any statistical difference?

4. How long a period of time is taken to complete the filling of the balloon? Is the process a painful one, such that anesthesia is required?

5. How much traction must be made upon the tenaculum to straighten the uterus as it appears in the x-rays, or does the pressure in the balloon system do this by acting as a splint?

6. What, exactly, are the "specific radiographic and manometric safeguards" which must be observed in performing the test? What happens if they are not observed? What difficulties were encountered with the balloon on which these studies are based, which make it necessary that a new model be prepared to "obviate many of the problems encountered in preceding models"? How does the "latest revision" differ from the balloon described in the paper, and what are the involved safeguards its use requires?

7. Among the "hypotonia cases," what is the evidence which proves that the preconceptional isthmic defect was in no case the direct result of tearing due to high pressure and that a subsequent late abortion was not a similar result?

8. What is the precise evidence supporting the statement that the more marked the isthmic "hypotonia" in the nonpregnant, the greater the tendency to abort early, and vice versa? Or is this coincidental? If not, is "isthmic hypotonia" considered a direct cause of early abortion?

9. What is the authors' definition of "depolymerization"? What is the histological test which is being used to detect this? Precisely what are the findings which permit the preliminary conclusion that "an effector substance [proeffacin] in the amniotic fluid of patients with manifest cervical incompetence and in active labor at term does exist"? In carrying out the experiments mentioned in this connection, how, exactly, was the amniotic fluid collected? How was the isthmic lavage carried out? How much amniotic fluid was used, and over what period of time? How were the tissues obtained for histological study (biopsy? hysterectomy?); Was the "depolymerization" instantaneous or delayed? If delayed, for how long? How many cases have been studied? What was the age range of the patients selected for this study? Is proeffacin found only in amniotic fluid, or may it also be found in blood, or serum, or tap water, or connective tissue ground substance, or cervical mucus?

10. Of the 46 patients having circlage during pregnancy, at what stage of pregnancy was this performed? Is the apparent difference in effectiveness between cervical and isthmic circlage truly significant? Subsequent to operation, what was the exact duration of pregnancy in the patients going into labor spontaneously? In how many cases exactly was the suture cut electively at "38 or 39 weeks"? The average weight of babies following "cervical circlage" was 2,180 grams, and it was 2,860 grams following "isthmic circlage." What was the range of figures of which these were an average, and are the two averages statistically different? Similarly, are the pregnancy durations following the two procedures significantly different? Success rate is based upon the number of babies who "lived." Were there any neonatal deaths?

11. The contraindications to "circlage," and the risks of the procedure during pregnancy are listed. How many cases were rejected as not

suitable? In how many of the 46 cases were any of the listed complications encountered? The over-all success rate is listed as 70 per cent. What exactly happened in the other 30 per cent? Repair during pregnancy has been reported before. How do these results compare with those of other techniques?

12. Fifty-eight "preconceptional operations" were done, and 36 were followed through a pregnancy. What of the other 22? Over what period of time, in terms of years, were these operations done? Repair prior to pregnancy has been reported before. How do the results of the double "isthmic circlage" compare with those achieved by simpler techniques in the hands of others?

13. Were there any postoperative complications following the preconceptional procedure?

14. The use of vasopressin has been largely abandoned as an adjunct in vaginal hysterectomy because of the high incidence of serious reactions. Were none encountered here?

15. If the "isthmus rather than the cervix is the primary sphincter of pregnancy," how may one explain the late abortions which inevitably follow high amputation of the cervix only, or lacerations extending only to the vaginal vault but not involving the isthmic segment?

16. In the 1959 article it is stated that "20 per cent of the [habitual abortion] patients in our series who were successfully treated by psychosomatic methods had theretofore recurrently aborted in the second trimester." Exactly how many patients does this represent? Does this imply that psychotherapy is a useful device in treating habitual late abortion? How many had isthmic "hypotonia"? In how many was the "hypotonia" corrected by psychotherapy?

To paraphrase the language of the Navy, these remarks should not necessarily be construed as derogatory. But I am sure that criticism of this work will be avoided by a clear and detailed exposition of the exact methods used, a forthright appraisal of the limitations, deficiencies, and hazards of the methods, a proper definition of the precise conditions under which the observations were made, and a complete listing of the number of observations and the exact results in each of the several groups and situations which are reported, with statement of the ranges and statistical evaluation where it is applicable.

Also, if all of the prior anatomical work is to be rejected as an *in vitro* artefact, it would

be helpful to cite actual, rather than inferential, proof showing conclusively that (1) isthmic contours are significantly and invariably altered by the conditions described in the anatomical studies, and (2) that the isthmic contours shown and cited here are not simple distortions resulting from the conditions of the experiments.

Finally, if the proeffacin inference is to be made, supporting data would be of much interest.

David N. Danforth, M.D.

636 Church St.
Evanston, Illinois
March, 1961

Reply by Dr. Mann

To the Editors:

I appreciate Dr. Danforth's critical reading of the recent paper on the uterine isthmus and, along with Dr. McLarn and Dr. Hayt, regret that many of the questions he raises were not more comprehensively covered. Our original

manuscript submitted to the editors included many of the details requested by Dr. Danforth but, in consequence, was rather more a monograph than an introductory article. The editors felt that a reduction in length, in the interest of both policy and clarity, was in order, particularly since the paper (subtitled Part I) represented but the first of a series of papers relating to the uterine isthmus.

With the introductory paper now published, forthcoming articles shall be less general and, hopefully, more to Dr. Danforth's liking.

Until these articles appear in print I trust that he will be content with our several discussions of the subject, the most recent of which entailed an entire afternoon of formal debate before the Michigan Society of Obstetrics and Gynecology last month.

Edward C. Mann, M.D.

The New York Hospital
525 East 68th St.
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April 20, 1961

Item

Certification by American Board of Obstetrics and Gynecology

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GYNECOLOGY

The human ovary in relation to aging

Protein characterization by the "pH signature" technique

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A KNOWLEDGE of chemical and morphological changes occurring in the ovary with relation to aging is fundamental to progress in many phases of gynecology. For some years we⁹ have been interested in applying histochemical and allied methods to the study of gynecological problems, including human^{8, 18, 19} and experimental^{10, 11} ovarian changes. As the latest essay in this field, we have applied the "pH signature technique"^{11, 6, 7, 29, 32} to a series of relatively normal ovaries in a range of patient age. This technique assists in characterizing protein structure of cellular components. For comparison a battery of connective tissue stains has been incorporated in the investigation.

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Materials and methods

During a period of 8 months, ovarian tissue was collected from various hospitals of Jacksonville, including the Baptist Memorial Hospital. Blocks of ovarian tissue obtained during regular surgical procedures were fixed in neutral buffered formalin. Only those cases were selected for study in which ovarian removal was secondary, there being no primary or significant ovarian lesions.

Fifty-three cases were found suitable for this investigation, and were divided into four age categories as follows: ages 20 to 33, 14 cases; ages 34 to 43, 26 cases; ages 44 to 53, 7 cases; ages 54 to 66, 6 cases.

Sections (3 μ) were cut from the formalin-fixed, paraffin-embedded blocks. These were staining with 5 by 10⁻⁴ M solutions of methylene blue C.I. No. 52015 (Harleco) or of light green, C.I. No. 42095 (Harleco) according to the technique of Dempsey and Singer^{3, 29, 30} as modified by Barrnett.¹ Methylene blue was employed at pH 3,4,5,6,7,8.

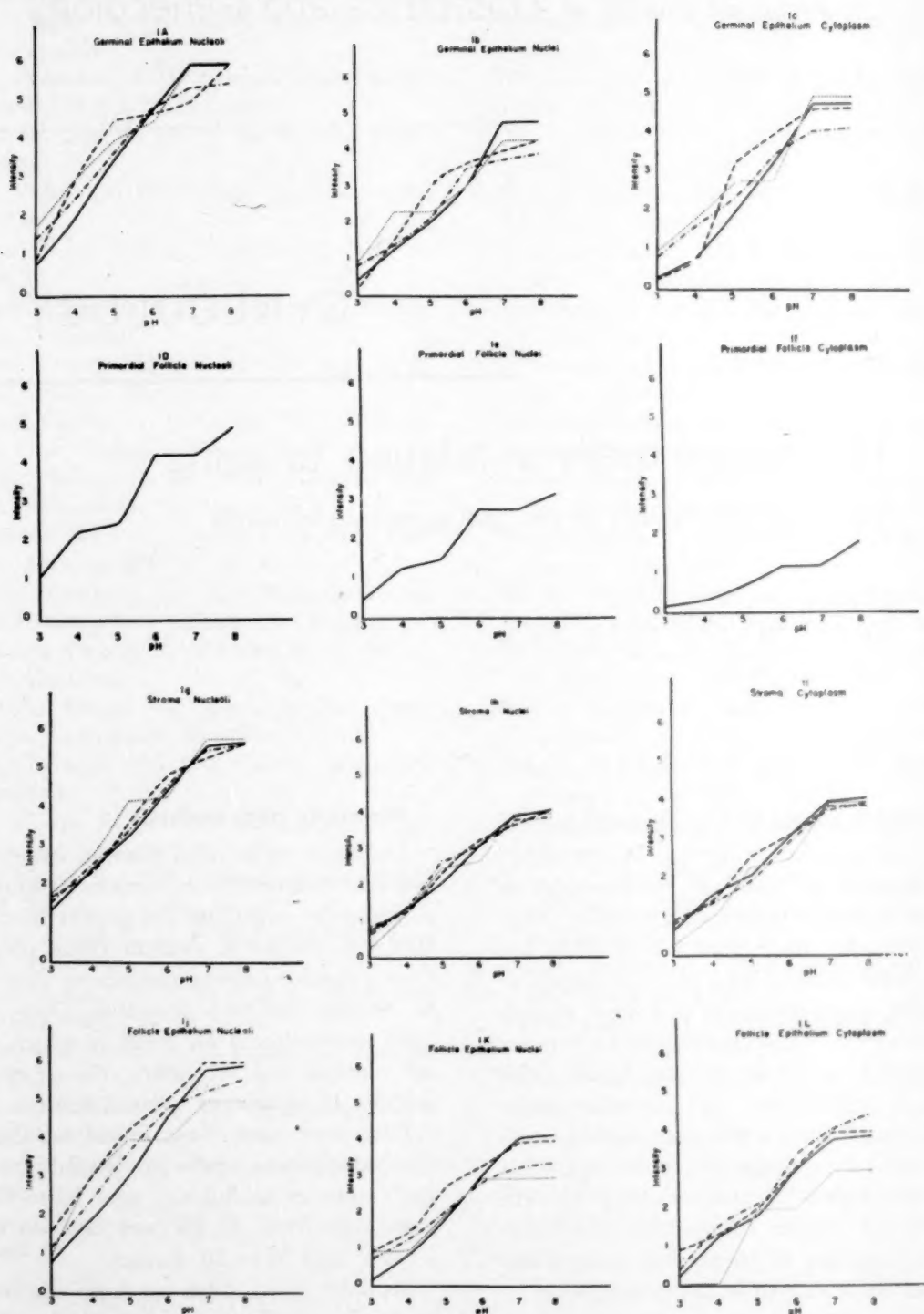


Fig. 1. Diagrams of intensity of methylene blue staining of various cellular components of ovaries in relation to patient age: Germinal epithelium nucleoli (*a*), nuclei (*b*), cytoplasm (*c*); primordial follicle nucleoli (*d*), nuclei (*e*), cytoplasm (*f*); stroma nucleoli (*g*), nuclei (*h*), cytoplasm (*i*); follicle epithelium nuclei (*j*), nuclei (*k*), cytoplasm (*l*).

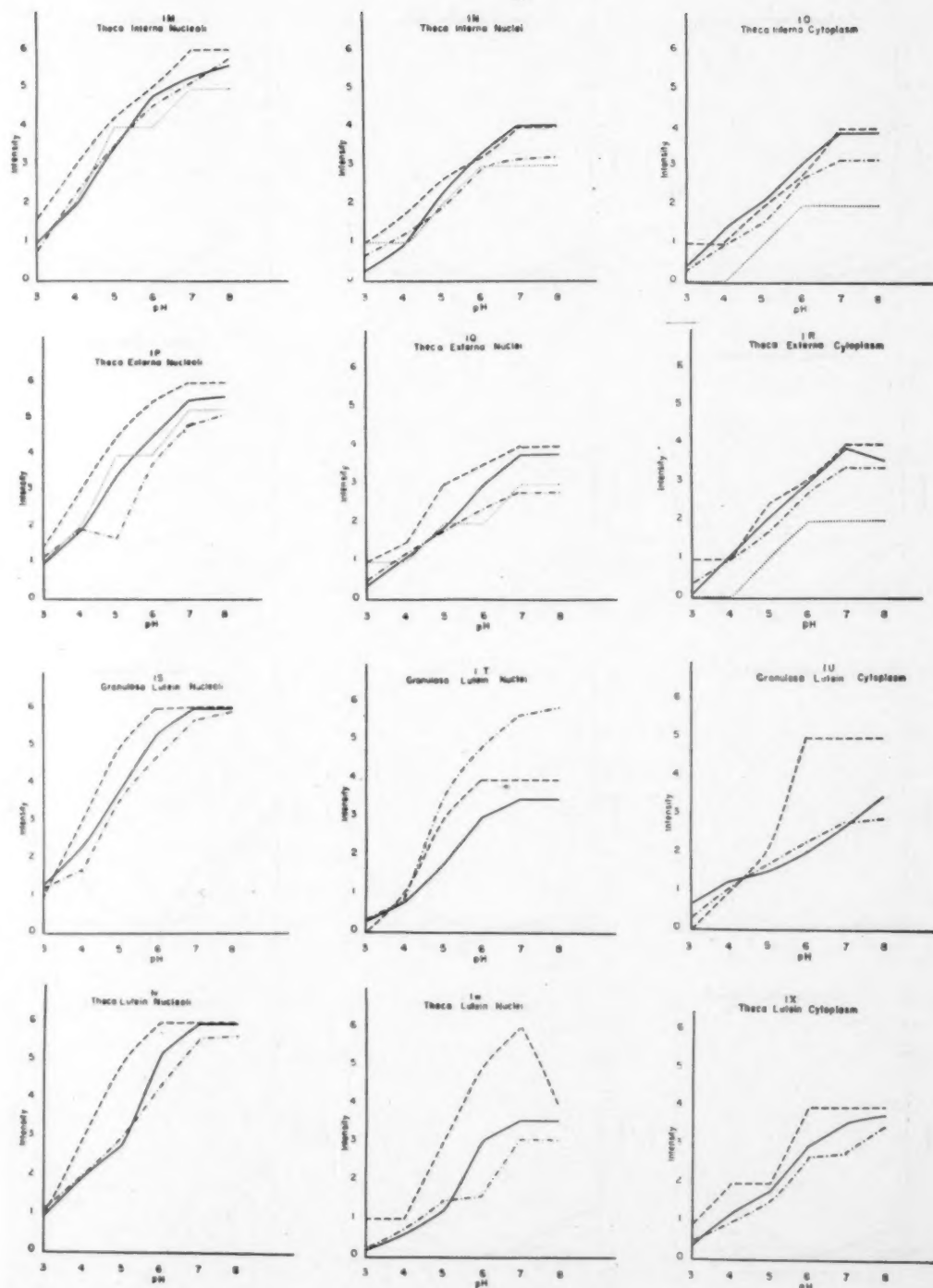


Fig. 1 (cont'd). Theca interna nucleoli (*m*), nuclei (*n*), cytoplasm (*o*); theca externa nucleoli (*p*), nuclei (*q*), cytoplasm (*r*); granulosa lutein nucleoli (*s*), nuclei (*t*), cytoplasm (*u*); theca lutein nucleoli (*v*), nuclei (*w*), cytoplasm (*x*). (Code similar in all figures: ages 20 to 33 —, 34 to 43 — — —, 44 to 53 - - - - , 54 to 65)

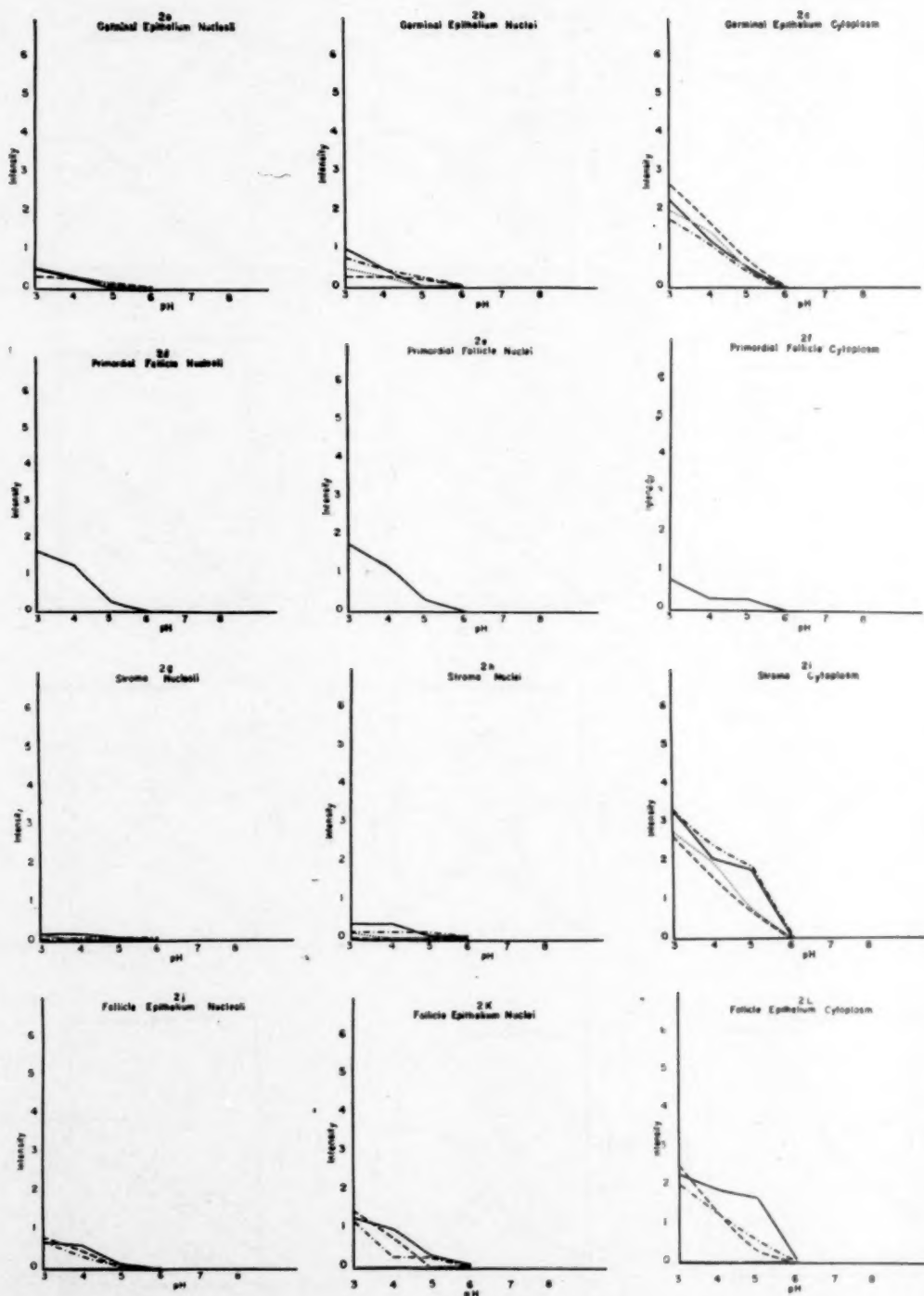


Fig. 2. Diagrams of intensity of light green staining of various cellular components of ovaries in relation to patient age: germinal epithelium nucleoli (*a*), nuclei (*b*), cytoplasm (*c*), primordial follicle nucleoli (*d*), nuclei (*e*), cytoplasm (*f*), stroma nucleoli (*g*), nuclei (*h*), cytoplasm (*i*); follicle epithelium nucleoli (*j*), nuclei (*k*), cytoplasm (*l*).

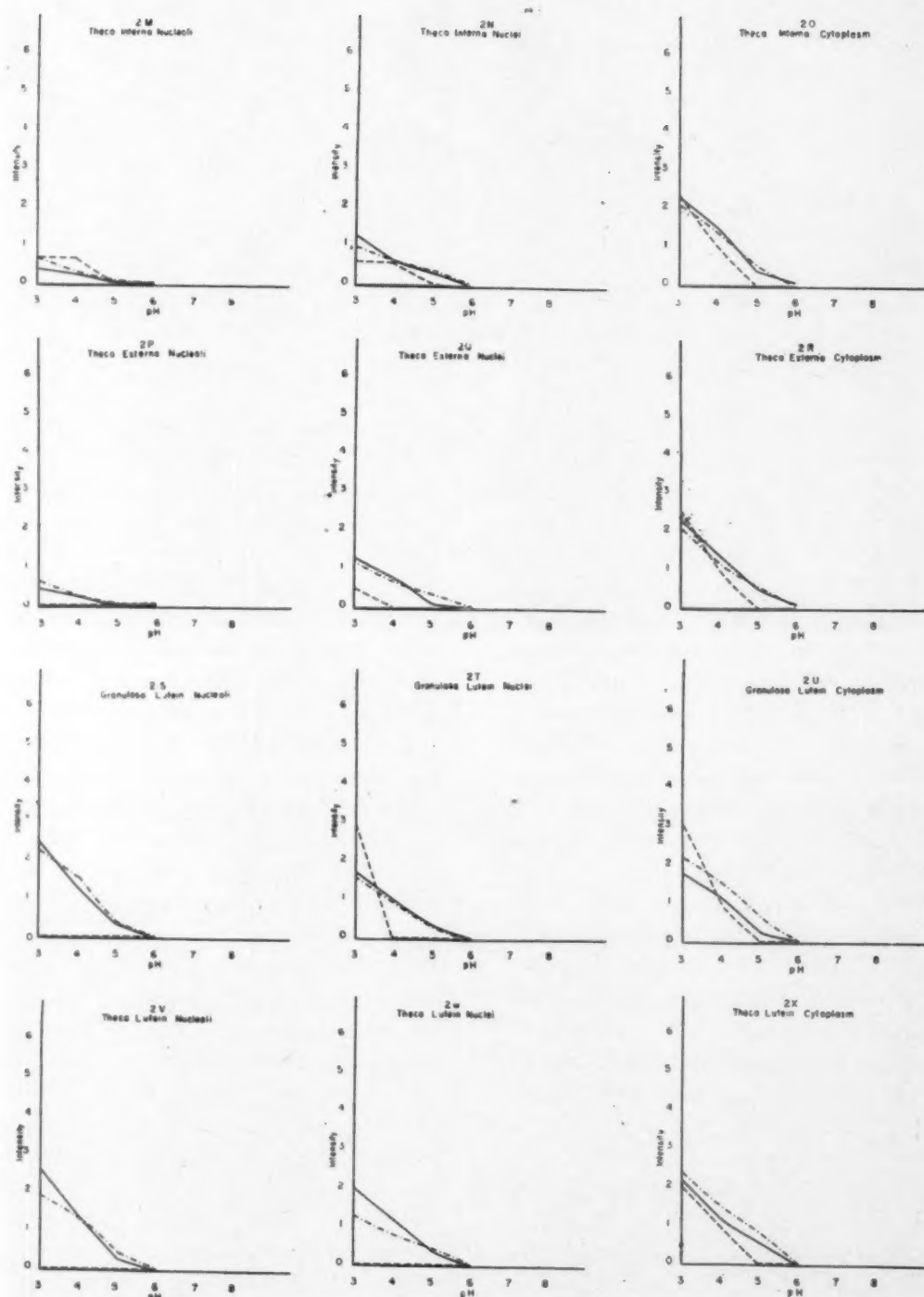


Fig. 2 (cont'd). Theca interna nucleoli (*m*), nuclei (*n*), cytoplasm (*o*); theca externa nucleoli (*p*), nuclei (*q*), cytoplasm (*r*); granulosa lutein nucleoli (*s*), nuclei (*t*), cytoplasm (*u*); theca lutein nucleoli (*v*), nuclei (*w*), cytoplasm (*x*).

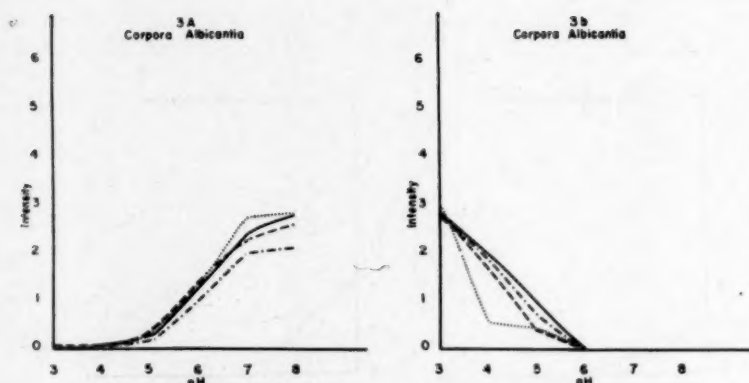


Fig. 3. Diagrams of intensity of staining of corpora albicantia in relation to patient age: (a) methylene blue; (b) light green.

Light green was employed at pH 3,4,5,6. Slides were stained overnight, dehydrated in alcohol and xylol, and mounted (H.S.R. mounting medium, Harleco).

Each section was examined and the staining characteristics of various cell structures evaluated on a subjective scale, ranging from 0 to 6. Generally the most intensely staining object with methylene blue at pH 8 was rated as 6, and everything else compared in general intensity of staining. Since the light green did not stain any individual structure as intensely as maximum methylene blue staining, rating of the light green stained sections was in general lower.

Additional sections from the same blocks were stained with hematoxylin and eosin, Masson's trichrome,^{24, 25} Verhoeff's elastic, Snook's reticulum, and periodic acid-Schiff²⁶ with diastase digestion.²⁵

The slides were examined without knowledge of the patient's age or clinical status.

Results

Staining intensity of the various ovarian structures is indicated in Figs. 1, 2, and 3. In general, methylene blue was strongest in high pH ranges, diminishing with lowering of pH. Light green was strongest at pH 3, falling rapidly at pH 4, and usually being virtually absent at pH 5 or above. Microscopic features of the study are illustrated in Figs. 4 to 12.

Germinal epithelium. No differences were found among the various age categories.

Nucleoli stained intensely in alkaline pH (Fig. 1, a), nuclei somewhat less (Fig. 1, b), and cytoplasm had approximately the same staining properties (Fig. 1, c) as nuclei. Nucleoli and nuclei stained very faintly with light green at pH 3 (Fig. 2, a and b), while cytoplasm stained somewhat more strongly (Fig. 2, c). A basement membrane was identified by the reticulum stain (Fig. 4, D) directly beneath the epithelium.

Primordial follicles (Fig. 5). Only in the age 20 to 33 group were these sufficiently numerous for readings to be taken, principally from lining epithelium. With methylene blue, there was a diminishing order of staining reaction from nucleoli (Fig. 1, d) to nuclei (Fig. 1, e) to cytoplasm (Fig. 1, f). With light green, nucleoli (Fig. 2, d) and nuclei (Fig. 2, e) stained moderately, with less staining of cytoplasm (Fig. 2, f). The ovum was faintly positive to the periodic acid-Schiff stain (Fig. 5, e). A definite basement membrane was present around each follicle (Fig. 5, F) as indicated by the reticulum stain.

Stroma. There were no differences in staining properties related to age. Nucleoli (Fig. 1, g) stained somewhat more strongly with methylene blue than did nuclei (Fig. 1, h) or cytoplasm (Fig. 1, i). With light green staining, nucleoli (Fig. 2, g) and nuclei (Fig. 2, h) were essentially invisible, but stroma stained rather strongly in acid ranges (Fig. 2, i). There was marked reticulum fiber staining (Figs. 4, D, and 5, F).

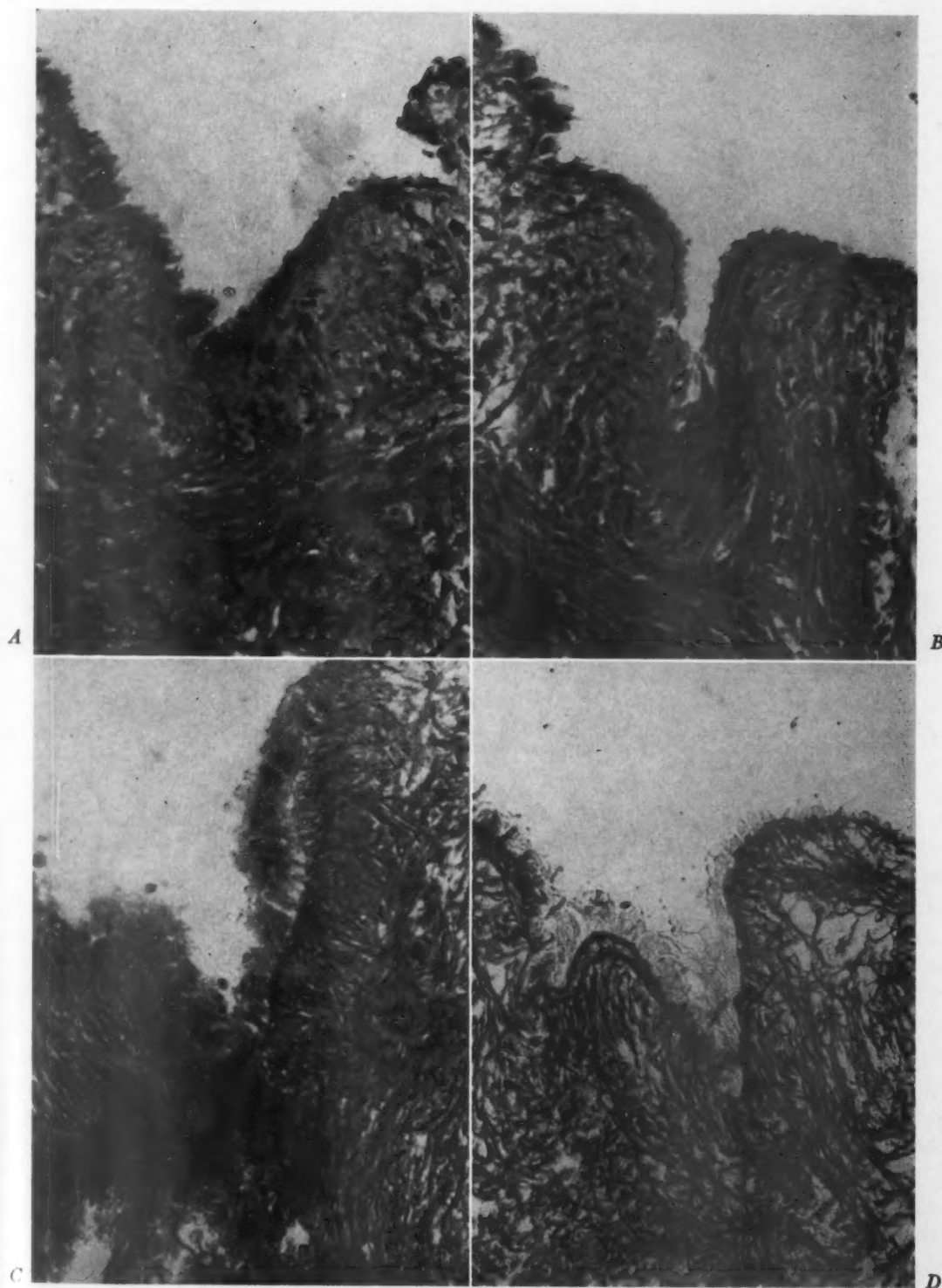


Fig. 4. Ovary from 25-year-old woman. Germinal epithelium, tunica albuginea, and stroma ($\times 330$). *A*, Methylene blue, pH 6. Strong nuclear and moderate cytoplasmic staining of all components. *B*, Methylene blue, pH 4. Somewhat weaker staining of nuclei and definitely weaker staining of cytoplasm of all components. *C*, Light green, pH 3. Only faint shadowing of epithelial nuclei. No nuclei visible in stroma in this photomicrograph, but fibers stain well. *D*, Reticulum. Marked staining of fibers in tunica albuginea and in immediately underlying stroma.

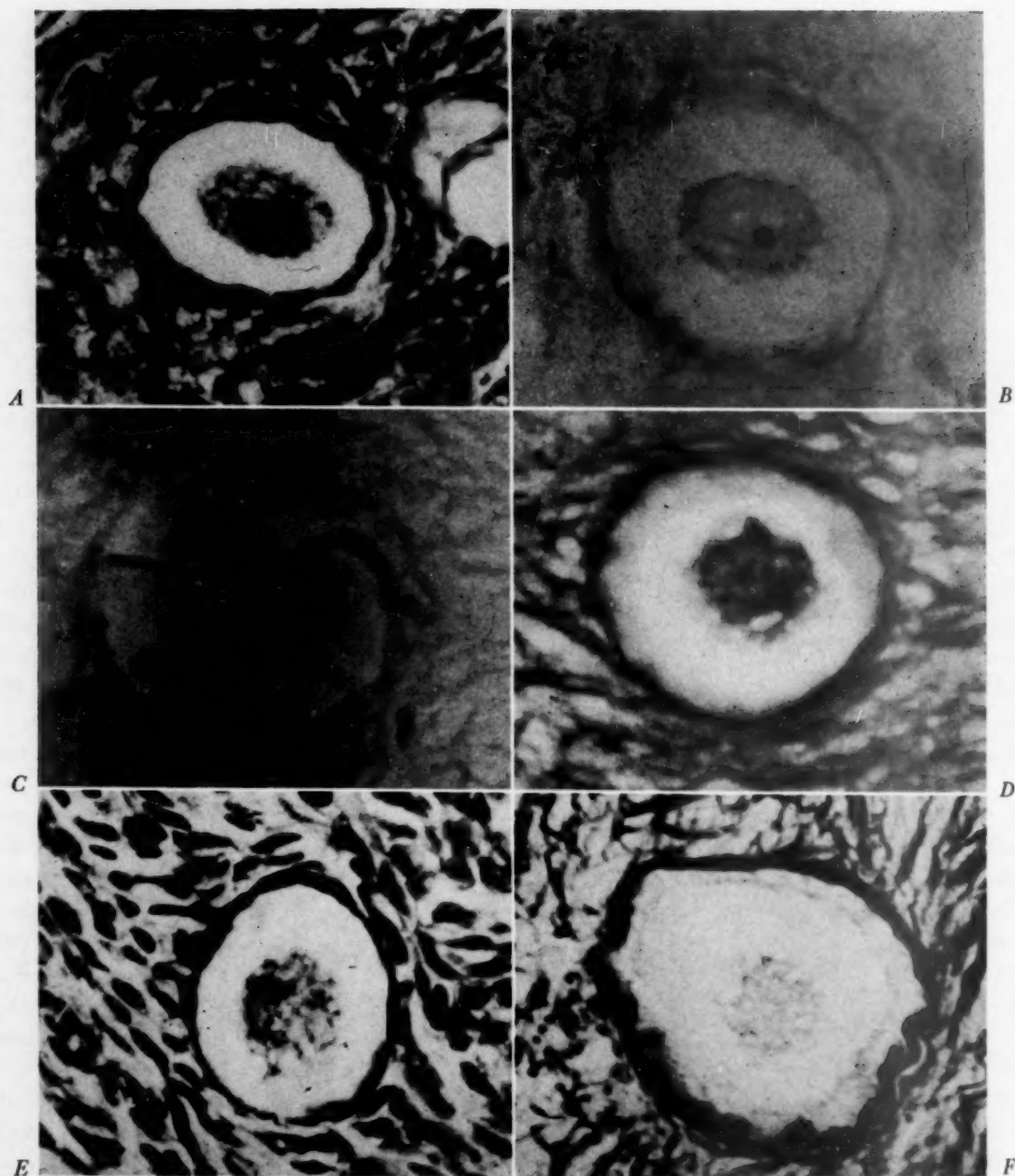


Fig. 5. Primordial follicles in ovary of 21-year-old woman ($\times 845$). *A*, Methylene blue, pH 8. The nucleus and nucleolus of the ovum, the nuclei of the follicular epithelium and of the stroma stain clearly. *B*, Methylene blue, pH 4. The nucleolus of the ovum still stains definitely, but most other cellular features are faint. (The black granules in the upper left corner are artifacts.) *C*, Light green, pH 5. The staining of all components is extremely faint. *D*, Light green, pH 3. There is moderate general staining of cytoplasmic, nuclear, and fibrillar material, without specificity for any structure. *E*, Periodic acid-Schiff, hematoxylin. Nuclear material in the ovum stains moderately. Hematoxylin staining of follicular and stromal nuclei. *F*, Reticulum. Strong fiber reaction around follicle, and in stroma.

The tunica albuginea showed somewhat lighter cytoplasmic staining than deeper lying stroma (Figs. 4 and 12). No numerical estimations of staining intensity of tunica albuginea were made.

Follicle epithelium. As anticipated, there were fewer follicles in the older age groups. Nucleoli (Fig. 1, *j*), nuclei (Fig. 1, *k*) and cytoplasm (Fig. 1, *l*) showed less staining intensity with methylene blue in the 54 to

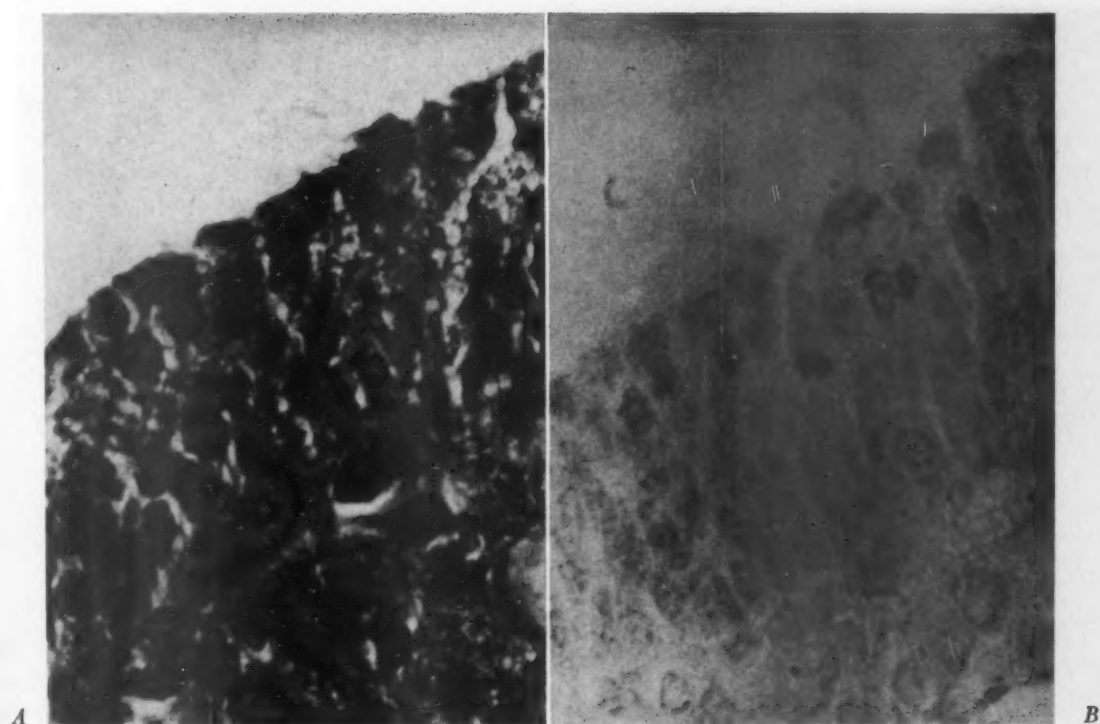


Fig. 6. Wall of developing follicle from ovary of a 44-year-old woman ($\times 845$). *A*, Methylene blue, pH 8. Marked staining of nuclear and cytoplasmic follicle and theca interna cells. Mitotic figure in follicle epithelium is densely stained. *B*, Methylene blue, pH 4. Mitotic figure in follicle epithelium is still strongly stained, while all other cellular elements show little affinity for methylene blue.

60 age groups than in younger age categories. No light green staining was identified in follicle epithelium (Fig. 2, *j, k, l*) in the older age group. Mitotic figures in follicle epithelium stained intensely with methylene blue in alkaline ranges (Fig. 6, *A*) and retained their staining intensity in more acid ranges when other structures were faint (Figs. 6, *B*, and 8, *B*). No numerical estimations of staining intensity of mitotic figures were made.

Theca interna. In developing follicles nucleoli in all age groups (Fig. 1, *m*) had greater affinity for methylene blue than did nuclei (Fig. 1, *n*) or cytoplasm (Fig. 1, *o*). Cytoplasm in the 54 to 60 age group stained less than that in younger age categories. There was some increase in staining progressively with light green from nucleoli (Fig. 2, *m*) to nuclei (Fig. 2, *n*) to cytoplasm (Fig. 2, *o*). No nucleoli were identified in the 54 to 60 age group with the light green stain. Moderate reticulum staining was present in theca interna and externa (Fig. 8, *D*).

Theca externa. Theca externa gave results closely corresponding to those of theca interna for both stains, as regards nucleoli, nuclei, and cytoplasm (Figs. 1 and 2, *p, q, r*).

Graafian follicles. These were not found in sufficient number for numerical estimate of staining intensity. The zona pellucida (Fig. 7, *A, B*) stained well with methylene blue, and intensely with periodic acid-Schiff routine (undigested and amylase digested). There was condensation of reticulum fibers (Fig. 7, *C*) around the expanding follicle.

Granulosa lutein (Fig. 9). Not enough corpora lutea were identified in the 54 to 60 age group for readings to be taken. Nucleoli stained intensely with methylene blue (Fig. 1, *s*), more than nuclei (Fig. 1, *t*), or cytoplasm (Fig. 1, *u*). There was considerable variation in nuclear and cytoplasmic staining among the age groups. However, within age groups staining quality of lutein cells varied with the stage of development. This may account for variations in reaction to light green

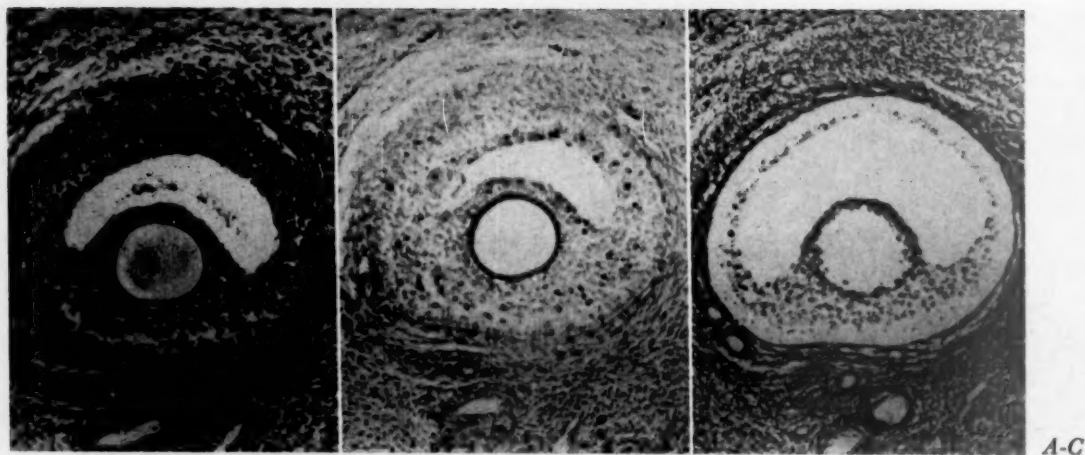


Fig. 7. Graafian follicle in ovary of 29-year-old woman ($\times 132$). *A*, Methylene blue, pH 7. Definite staining of nucleus of ovum, zona pellucida, and nuclei of follicle epithelium, theca interna and externa. *B*, Periodic acid-Schiff. Strong staining of zona pellucida. *C*, Reticulum. No reticulum within follicle, but many fibers demonstrated in theca interna and externa.

as well (Fig. 2, *s, t, u*). Fine reticulum fibers ran between the lutein cells.

Theca lutein. Results closely paralleled (Figs. 1 and 2, *v, w, x*) those for granulosa lutein. Paralutein cells were not identified with sufficient regularity for readings to be made.

Corpora albicantia (Figs. 10 and 11). The corpora albicantia showed moderate affinity for methylene blue in alkaline range (Fig. 3, *a*) and for light green (Fig. 3, *b*) in alkaline range. There were no striking differences associated with the age category.

Germinal inclusion cysts (Fig. 12). The lining epithelium of these showed the same staining properties as surface germinal epithelium (Figs. 1 and 4). The cyst content showed considerable blue staining with methylene blue, and in more acid ranges had a deep blue-lavender hue. There was little reaction with light green. Intense red staining occurred with the periodic acid-Schiff routine, unaffected by amylase digestion.

Comment

Most of the results of this study are related to the distribution of proteins in the ovary, including nucleoproteins. Other ovarian constituents, including lipids and carbohydrates (except for the polysaccharide in inclusion cysts), were leached out by the variety of watery and organic solvents in-

involved in tissue preparation. Probably a significant proportion of protein had been removed also. Much of that remaining may have been altered in molecular structure. Proteins are the most important component in the molecular organization of cells and are indispensable in the maintenance of vital processes.⁴ Proteins in solution are amphoteric.²⁰ Their basic and acidic groups, by their dissociation, give rise respectively to positive and negative charges on the protein molecule. These groups include the free side groups of certain amino acids (e.g., basic—lysine, histidine, arginine; acidic—glutamic, hydroxyglutamic, and aspartic acids, tyrosine, serine) and charged substances which may be conjugated to the protein. Proteins differ according to the nature and number of their constituent amino acids and their conjugated substances. Free basic groups may be relatively more abundant in one protein, and acidic groups in another. The ability of proteins to take up acid or basic dye according to the pH of the environment is an expression of their amphoteric properties and the charge on the dye ion.²⁰ The degree of staining at various pH levels, including the pH at which the protein ceases to bind dye, evidently reflects the dissociation characteristics of the protein.²⁰ Curves of dye binding may be employed to characterize solid proteins.

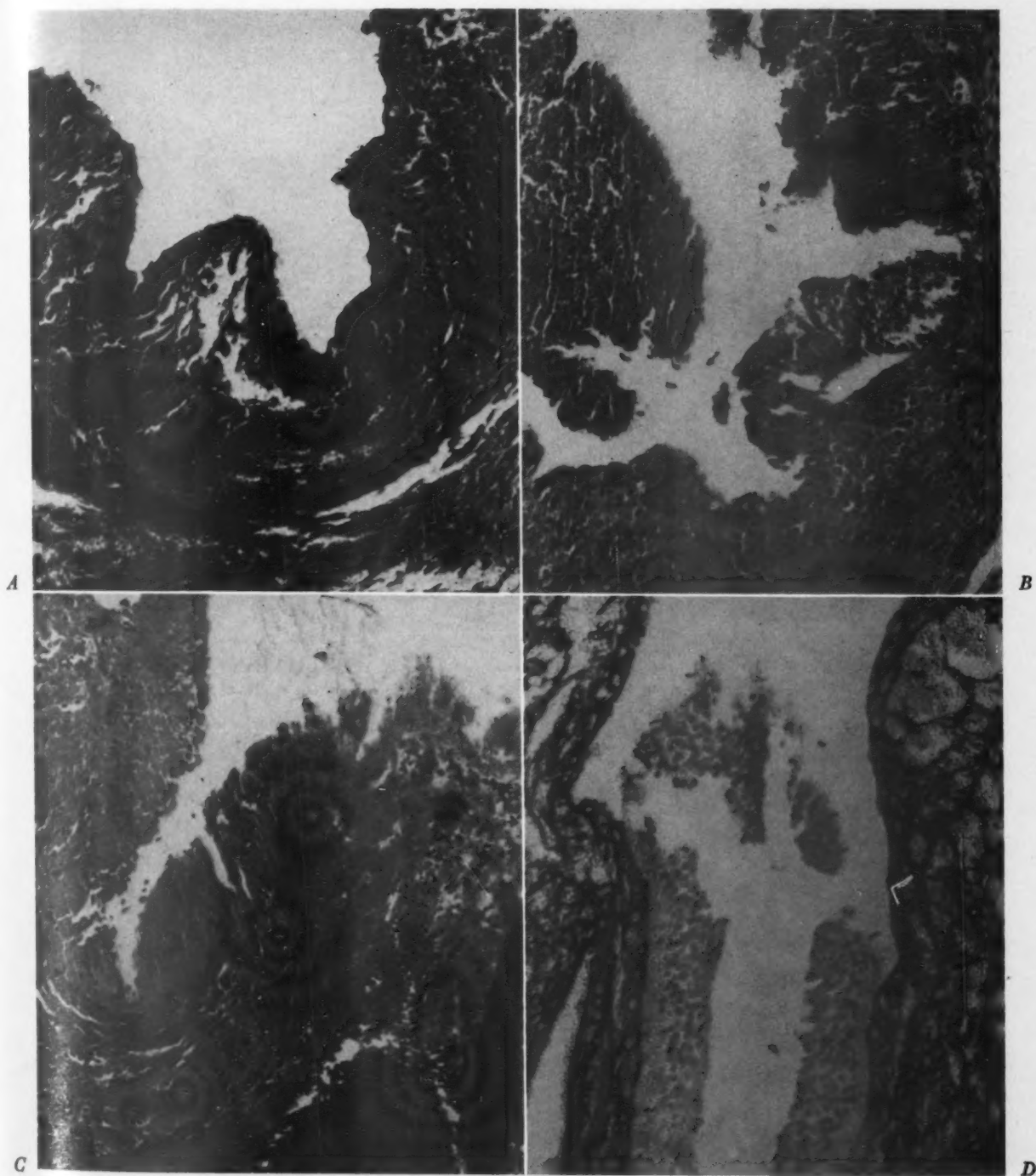


Fig. 8. Ruptured follicle from 43-year-old patient ($\times 132$). *A*, Methylene blue, pH 7. Marked nuclear staining of follicle epithelium, theca interna and externa. *B*, Methylene blue, pH 4. Mitotic figures in follicle epithelium are still prominent, even though staining of other elements is much weaker. *C*, Light green, pH 3. Moderate nonspecific staining of all tissue elements, with heavier staining of red blood cells in vessels. *D*, Reticulum. No reticulum in follicle epithelium, but theca interna and externa have definite reticulum pattern.

Nucleoproteins are an important constituent of cells. They result from the combination of nucleic acids and proteins. In certain cells they constitute the major portion of

the solid material.⁴ Structures containing nucleic acids are basophilic because of the presence of free phosphate groups.²⁰ A basic dye, such as methylene blue in the present

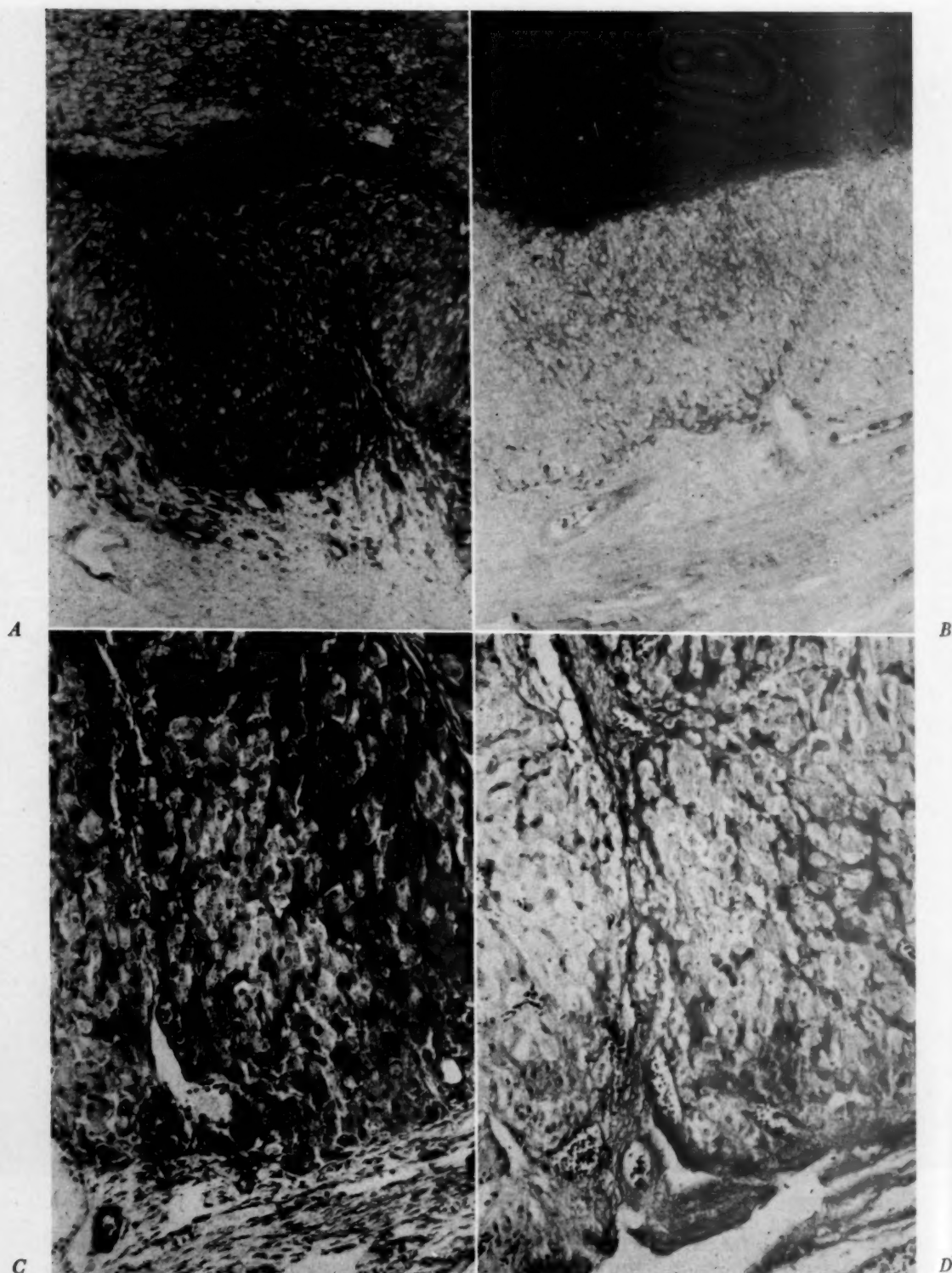


Fig. 9. Early corpus luteum in ovary of 36-year-old woman. *A*, Methylene blue, pH 8 ($\times 33$). Moderate nuclear staining of granulosa lutein cells. Fibrin and blood moderately stained. *B*, light green, pH 3 ($\times 33$). Cellular elements are quite faint, but fibrin and blood are heavily stained. *C*, Methylene blue, pH 8 ($\times 132$). Moderate nucleolar and nuclear staining of lutein and paralutein cells, with variable cytoplasmic staining. *D*, Light green, pH 3 ($\times 132$). All cellular elements except red blood cells are relatively faint.

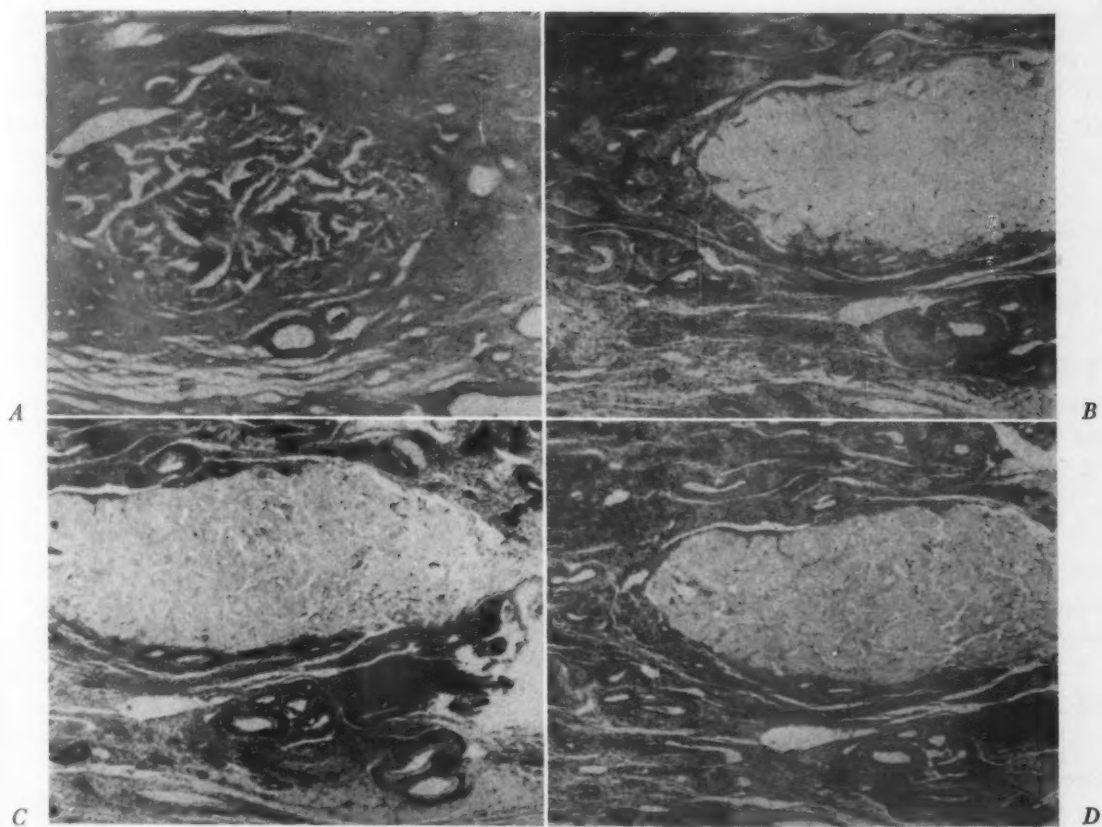


Fig. 10. Corpus albicans in ovary from 41-year-old woman ($\times 33$). *A*, Methylene blue, pH 7. Corpus albicans stains much lighter than adjacent stroma. *B*, Light green, pH 3. Corpus albicans stains slightly heavier than adjacent stroma. *C*, Elastic stain. Elastic fiber staining is seen only in walls of vessels. *D*, Periodic acid-Schiff, amylase digested. Rather light staining of corpus albicans as compared to stroma and vessels.



Fig. 11. Atrophic ovary from 59-year-old woman ($\times 33$). *A*, Methylene blue, pH 4. Relatively thin cortex shows dense staining as compared to deeper lying corpus albicans. *B*, Light green, pH 4. Faint staining of stroma and corpus albicans as compared to erythrocytes in vessels.

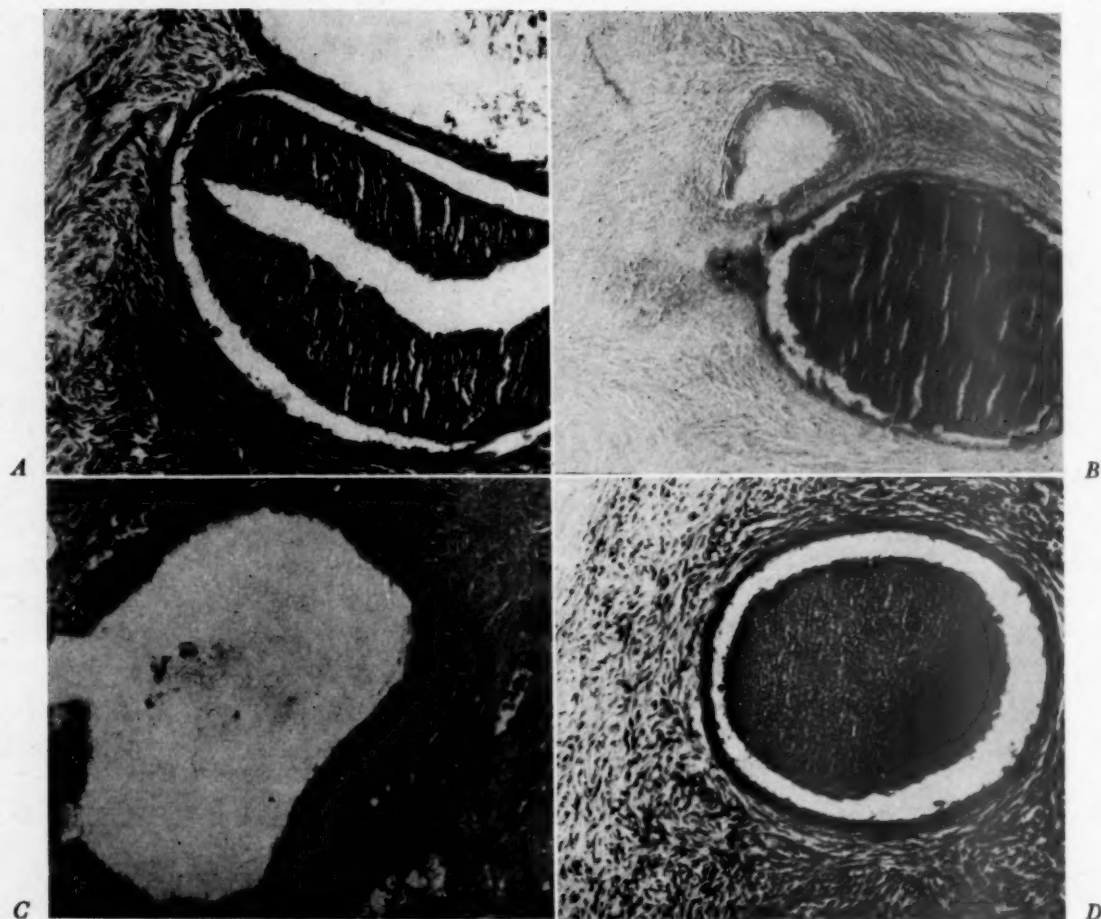


Fig. 12. Glandular inclusion cysts in ovary of 29-year-old woman ($\times 132$). *A*, Methylene blue, pH 8. Heavy blue staining of cyst content, of lining epithelium, and of germinal epithelium on surface of ovary. Tunica albuginea is less heavily stained than underlying stroma. *B*, Methylene blue, pH 3. Cyst content is heavily stained, with slightly lavender hue, exhibiting phenomenon of "metachromasia." *C*, Light green, pH 3. Essentially no staining of cyst content, whole tissue structures show moderate staining. *D*, Periodic acid-Schiff, amylase digested, hematoxylin counterstain. Cyst content shows heavy red staining. This reaction after amylase digestion, suggests that the content is a polysaccharide. Considering the "metachromasia" noted in *B*, the cyst content is probably a mucopolysaccharide.

study, may be applied for the staining of these structures. Ordinarily, such staining will not distinguish between the classes of nucleic acids, or between nucleic acids and other acid substrates.

Comparisons have been made of nuclear desoxyribonucleic acid (DNA) in normal and malignant human cells. Leuchtenberger and co-workers²³ found that interphase nuclei from precancerous and malignant tissues reveal much greater DNA scatter from cell to cell than do the nuclei from the normal homologous tissues. In the present study, mitotic figures from follicle epithelium (Fig. 6) retained affinity for basic dye

in relatively acid solution when nucleoli and nuclei of adjacent cells stained lightly. We have previously made similar observations in mitotic figures in squamous cell carcinoma of the cervix,³² adenocarcinoma of the colon,⁶ and squamous and basal cell carcinoma of skin.⁷ Studies in various types of cells² on DNA synthesis have usually placed it during the mitotic cycle. This also suggests increased concentration within the mitotic figure. Resting cells have usually a rather constant DNA content.²²

Our staining intensity evaluation, assigning arbitrary units, is rather subjective. Properly designed photometric methods for

each of the cell components might have had certain theoretical advantages, but did not seem feasible. We tried to concentrate on staining intensity per unit area (e.g., per square micron) of each structure and not be swayed by the relative size of the object under examination.

The intense staining reaction of the zona pellucida (Fig. 7) is of interest. This structure was not present with sufficient frequency for estimations of staining intensity on a numerical basis. Previously, we found similar positive periodic acid-Schiff reaction in the rabbit ovary in pregnancy¹¹ and otherwise.¹⁰ Harter¹⁶ found similar reaction in the zona pellucida of the rat, which he characterized glycoprotein. Variations exist in microscopic delineation of the zona pellucida.^{13, 28, 31} More exact understanding of the chemical, as well as the morphologic, nature of the zona pellucida may clarify knowledge of enzymatic²⁸ and other processes involved in ovulation and implantation.

Reactions of cyst fluid in glandular inclusions (Fig. 12) suggest this to contain mucopolysaccharide. Production of a lavender hue after application of methylene blue is an example of metachromasia. We⁶ observed similar metachromasia with the "pH signature" technique in mucin occurring in normal and adenocarcinomatous colonic mucosa. Variable patterns of metachromasia have been reported in different epithelial mucins by various investigators employing varied staining techniques.¹⁴ Fisher⁵ found the content of "pseudomucinous" cystomas and cystadenomas to have the same reaction to a battery of histochemical procedures as mucin. In 1953 we⁸ described intense evidence of dehydrogenase activity in the epithelium of cortical glandular inclusions.

In a study from our laboratory, recently Joel¹⁰ found that the green component of Masson's trichrome^{24, 25} became more intense in older, more densely hyalinized corpora albicantia. This was a function of the age of the individual corpus albicans, not of the patient. The light green stain employed in the present study is very closely akin to that of the trichrome procedure. We

did not attempt to classify corpora albicantia in the present investigation, but our subjective observations are in accord with Joel's findings on this point. Dehydrogenase activity⁸ is not present in the inactive corpus albicans, whereas it has been demonstrated in varying degree in stroma, follicle epithelium, and corpora lutea.

As in other recent studies from our laboratory,^{18, 19} the specific techniques of the present study did not reveal striking differential features of ovaries related to aging. There are certain recognized ovarian morphological changes with aging^{17, 18, 19, 21, 27} which were present in the material of our current study. Our staining reactions were in general the reflection of these morphological alterations (their presence, absence, or microscopic pattern) and not primary phenomena.

In the next phase of this study, we plan to estimate mass and allied phenomena of ovarian constituents in relation to aging, using interferometry.¹²

Summary

In a continuing study of aging changes in the human ovary, the "pH signature" technique has been applied. This technique assists in the characterization of proteins. In general the staining reactions reflected previously described morphological changes with aging. Certain specific findings appeared:

1. Mitotic figures in follicle epithelium showed marked affinity for methylene blue in relatively acid ranges.
2. The zona pellucida in Graafian follicles was strongly positive to the periodic acid-Schiff stain, suggesting a polysaccharide component.
3. Fluid in germinal inclusion cysts showed reactions of mucopolysaccharides.

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Surgical management of acute pelvic infection refractory to conservative therapy

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THE MANAGEMENT of acute pelvic infections has been a distinct challenge to physicians in general and to gynecologists in particular since time immemorial. The early writings of Hippocrates and those of Varandaeus quoted by Ricci¹ mention inflammation of the pelvic organs and its associated prognosis, morbidity, and mortality. Prior to the advent of antibiotics and chemotherapy the main therapeutic attack consisted of antipyretics, sedatives, bed rest in the semi-Fowler position, local heat to the pelvis, hot douches, and other general supportive measures. Under this conservative management many cases responded satisfactorily and left the patients relatively asymptomatic.

The discovery of penicillin by Fleming² in 1929 opened up a new avenue of therapeutic approach. The 1930's saw the sulfonamides appear and flourish.³ Dubos⁴ discovered tyrothricin in 1939. Penicillin was subsequently purified,⁵ and modified⁶ and, since that time, further discoveries have added still more agents to our antibiotic therapeutic armamentarium so that at the present time we have a vast number of specific antibiotic medications available to combat the scourge of pelvic infection.

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This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

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Originally it was considered that cortisone was contraindicated in the presence of infection because of its lytic action on inflammatory response and inhibition of granulation tissue.⁷ However, the subsequent studies of Hurtig,^{8,9} Matthews,¹⁰ and Collins¹¹ have shown the remarkable effect of this agent in resolving acute pelvic infections when combined with specific antibiotic agents.

However, both prior to and following the introduction of antibiotic and chemotherapeutic agents, there existed those cases which appeared "refractory" to treatment and which frequently resulted in the patient's death. For the most part, these represented cases in which the pelvic infection localized in the form of one or more loculated abscesses. When these localized and "pointed" so that they could be drained surgically through either the cul-de-sac or abdominal wall the efficacy of such a procedure became immediately apparent. On the other hand, when there was no evidence of clinical improvement despite intensive conservative therapy (the mass or masses failed to decrease in size or revealed evidence of rupture), it became readily apparent that a more drastic course of action was necessary. When nothing more was done, the resultant mortality as mentioned by Collins and Jansen¹² ranged from 85 to 90 per cent.

During the last decade a possible solution to the successful management of these refractory cases seems to have been found. Active surgical intervention in the face of acute and sometimes fulminating infection has in

essence reversed this mortality figure to its present 10 to 15 per cent level. This surgical attack as advocated by Collins and Jansen,¹² de Alvarez and Figge,¹³ TeLinde,¹⁴ and others¹⁵⁻¹⁷ must be thorough and complete. In general the procedure consists of surgical removal of the abscess area, removal of all spillage material by irrigation and suction, plus unilateral or bilateral salpingo-oophorectomy and total abdominal hysterectomy when technically possible.

Our experience at this hospital in the management of refractory pelvic infections has been recently reviewed and provides the material for this presentation.

Material

All admissions to the Gynecology Service of the United States Naval Hospital, San Diego, California, for the 3 year period from June, 1956, through July, 1959, were reviewed. All cases admitted with a diagnosis of acute pelvic inflammatory disease, or those subsequently found to have acute pelvic infections were studied in detail as to method of management, clinical course, and subsequent outcome. All patients with a persistent or increasing morbidity revealing irrevocable signs of overwhelming and life-endangering sepsis who, in the opinion of 2 or more gynecology staff members were not responding to intensive medical management, were considered "refractory" to conservative therapy. The pertinent clinical data, subsequent management, and ultimate outcome of 9 such "refractory" patients provide the basis for this preliminary report.

Findings

During the 3 year period studied, there were 4,543 admissions to the Gynecology

Service of our hospital. Of this number, 87 were admitted with or were found subsequently to have acute pelvic infections. Table I contains the total number of gynecology admissions per year plus the over-all incidence of pelvic infections as well as those considered refractory to conservative management. Our incidence of acute pelvic disease, although slightly higher than most private hospitals,^{13, 15} is lower than that found in most charity and county institutions.^{13, 14, 16} The incidence of "refractory" cases in this study is significantly lower than that reported by others.^{13, 16, 17} This would tend to substantiate the efficacy of our medical management in most cases of acute pelvic infection.

Table II contains the pertinent background data and significant past history of the 9 patients studied. Considering age first, it will be noted that there is a wide range between 18 and 45 years. It is commonly believed and frequently reported^{13, 16, 18, 20, 21} that pelvic inflammatory disease is more common in the early reproductive years. A review of all of our admissions would tend to confirm this fact, since the average age of our whole group of 87 patients was 27.6 years. However, in the 9 "refractory" patients it will be noted that over 50 per cent are 40 years or over. This is indeed interesting and could lead to speculation regarding the relationship of age and adequate response to antibiotic therapy.

Gravidity and parity are likewise recorded in Table II. Our findings in this regard reveal nothing unusual. Nulligravidas and multiparas are both represented and this is in close agreement with others.^{18, 19, 21}

Table II also outlines the pertinent background history in the 9 "refractory" patients studied. It is interesting to note that in all

Table I. Incidence of acute pelvic infections and refractory cases

Period studied	Gynecology admissions	Pelvic infections		Refractory cases	
		No.	%	No.	%
July, 1956, to June, 1957	1,401	22	1.6	1	0.07
July, 1957, to June, 1958	1,548	26	1.7	4	0.26
July, 1958, to June, 1959	1,594	39	2.4	4	0.25
Total	4,543	87	1.9	9	0.10

Table II. Pertinent background history

Case	Age	Gravidity	Parity	Abortions	Date admitted	Pertinent background history
1. (E. L. B.)	36	1	1	0	5/9/57	Two year history of recurrent pelvic infections
2. (J. S. S.)	18	0	0	0	10/14/57	6 month history of intermittent pelvic pain and questionable right adnexal mass
3. (C. R. H.)	24	4	4	0	10/21/57	Abdominal hysterectomy 12 days previously by private physician; indicated by near fatal peritonitis following last delivery
4. (M. V. E.)	44	1	1	0	2/6/58	Recurrent pelvic infections of 12 years' duration; transferred from private hospital following 30 days' therapy for "blocked bowels"
5. (A. H. G.)	40	3	0	3	3/3/58	One episode of pelvic infection 7 years previously treated conservatively without recurrence
6. (M. A. H.)	43	3	2	1	7/29/58	Recurrent pelvic infections for 13 years: curettage, conization, and colpoplasty-colpoperineoplasty 40 days previously
7. (P. A. G.)	45	4	1	3	11/22/58	Recurrent pelvic infections for 20 years: curettage and conization 11 months previously; tuboovarian abscesses drained vaginally 4 and 2 weeks previously
8. (A. S. W.)	38	4	3	1	3/19/59	Normal parturition 11 months previously; recurrent pelvic infections since; asymptomatic left adnexal mass for 2 months
9. (M. A. V.)	42	2	1	1	3/26/59	No previous history of pelvic infections; ruptured appendix at age 16 years

but one case the history of recurrent pelvic infection was present or suggested. This is in complete agreement with the commonly accepted concept that pelvic inflammatory disease is a chronic and recurrent problem caused and aggravated by invasion, either physiologic or instrumental, of the female genital tract.

In Table III are listed the clinical findings present on admission. These are, for the most part, self-explanatory and in complete agreement with those described by other investigators.^{13, 16-18, 19-21} Fever, tachycardia, and pelvic pain with or without nausea and vomiting are the significant symptoms of this entity. In the early and less acute forms of the disease the pelvic findings may not be too striking. However, as the disease progresses into the more acute phase and to the "refractory" stage the pelvic findings are definite and unmistakable.

An analysis of the period of conservative

management is presented in Table IV. During this period the patients were treated intensively with antibiotics, antipyretics, intravenous fluids, and blood transfusions if indicated. General supportive measures such as complete bedrest (modified semi-Fowler position), sedatives, analgesics, and local heat were administered. When localization or "pointing" of abscess pockets was evident, they were drained when possible by colpotomy. At time of admission cultures were obtained on the cervical secretions or purulent drainage from each patient. Pending the results of such cultures, broad-spectrum antibiotics were started subject to change when the sensitivity pattern was eventually determined. In most instances penicillin and streptomycin were used because of their specific antibacterial action.^{3, 5, 6} Two patients (4 and 6) were transferred to our activity from other hospitals which serves to explain both the pro-

Table III. Findings on admission

Case	Temperature	Pulse	Blood pressure	Pelvic findings
1 (E. L. B.)	103.2°	100	100/60	Right 10 by 10 by 10 cm. adnexal mass
2 (J. S. S.)	101.2°	124	118/70	Right 10 by 12 by 12 cm. adnexal mass
3 (C. R. H.)	100.2°	112	108/60	Active bleeding and purulent drainage from vaginal cuff; generalized induration and tenderness; infected abdominal wound
4 (M. V. E.)	101.8°	100	100/60	Bilateral 8 by 8 by 8 cm. adnexal masses (originally considered ovarian malignancies with inflammatory and necrotic changes)
5 (A. H. G.)	101.8°	140	140/100	Solitary 17 by 17 by 20 cm. mass filling the whole pelvis
6 (M. A. H.)	102.8°	112	98/68	Bilateral 10 by 10 by 10 cm. adnexal masses
7 (P. A. G.)	101.6°	110	126/70	Bilateral adnexal induration and tenderness; copious purulent drainage from vaginal colpotomy wounds
8 (A. S. W.)	100.2°	100	140/84	Left 15 by 15 by 20 cm. adnexal mass
9 (M. A. V.)	102.0°	120	130/80	Right 10 by 12 by 14 cm. adnexal mass

Table IV. Conservative management data

Case	Duration of treatment prior to admission (days)	Organism cultured	Antibiotic therapy	Duration of conservative management (hours)
1 (E. L. B.)	2	<i>Staphylococcus aureus</i>	Intravenous tetracycline HCl	48
2 (J. S. S.)	2	Anaerobic staphylococcus	Intramuscular procaine penicillin and streptomycin	10
3 (C. R. H.)	12	<i>Staphylococcus albus</i> , anaerobic streptococcus	Intramuscular procaine penicillin, streptomycin, oral chloramphenicol, and erythromycin*	40
4 (M. V. E.)	43	<i>Staph. aureus</i>	Intravenous aqueous penicillin, intramuscular procaine penicillin, and streptomycin*	288 (12 days)
5 (A. H. G.)	3	<i>Escherichia coli</i>	Intramuscular procaine penicillin and streptomycin, intravenous tetracycline HCl	30
6 (M. A. H.)	11	<i>E. coli</i>	Intravenous followed by oral chloramphenicol†	6
7 (P. A. G.)	2	<i>E. coli</i>	Intravenous aqueous penicillin, intramuscular streptomycin, and oral chloramphenicol	36
8 (A. S. W.)	3	<i>Staph. aureus</i>	Intravenous erythromycin, intramuscular procaine penicillin, and streptomycin	24
9 (M. A. V.)	6	<i>Alcaligenes faecalis</i>	Intravenous aqueous penicillin, intramuscular procaine penicillin, and streptomycin	32

*Oral broad-spectrum antibiotics at civilian hospital.

†Oral broad-spectrum antibiotics followed by intramuscular penicillin and streptomycin at transferring activity.

longed duration of symptoms prior to admission and the antibiotic coverage used. The duration of the period of conservative medical management is, likewise, found in Table IV. This ranged from 6 to 48 hours. The decision to terminate the period of conservative management in favor of active surgical intervention was based upon the patients increasingly moribund state, evidenced by the presence of septic shock and generalized peritonitis produced by either rupture of a previously localized abscess, or intractable bleeding.

Table V contains both the findings at time of operation and the extent of the surgical procedure performed. The high incidence of ruptured tuboovarian abscess and/or multiple pockets of purulent material noted at operation served to justify the nature of the preoperative course. As will be noted, Patient 3 (C. R. H.) had an abdominal hysterectomy 12 days previously at another hospital. Her immediate postoperative course was complicated by generalized pelvic and abdominal wound infection. Shortly after admission to our hospital, the infection caused erosion into a branch of the right uterine artery with resulting hemorrhage which necessitated laparotomy for ligation and control.

The extent of each surgical procedure performed is noted in Table V. This we feel is in keeping with the best surgical principles as outlined by Collins,¹² de Alvarez,¹³ TeLinde,¹⁴ and others.^{16, 17, 19, 21, 22} When an operation of this nature is indicated, it should be as complete as possible. An en bloc panhysterectomy with removal of both adnexa and appendix is the procedure of choice. When this is technically impractical or impossible excision of the local abscess is accomplished. Since the purulent exudate is generally already widely disseminated, we favor thorough irrigation of the peritoneal cavity to assure evacuation of all small loculated areas and all possible purulent exudate. The instillation of antibiotic agents into the peritoneal cavity has not been considered essential and has not been done routinely. Adequate drainage of the pelvis following

operation is considered very important. In cases of en bloc panhysterectomy and bilateral salpingo-oophorectomy drainage is accomplished through the open vaginal cuff by means of Pezzar catheters or a Chaffin-Pratt suction apparatus. When a tubo-ovarian abscess alone is removed, because of technical difficulties or poor condition of the patient, the abscess cavity is drained with a Chaffin tube which is brought out either through the cul-de-sac or through a stab wound in the flank. In addition, we have found it of value to place drains in both the subfascial and subcutaneous layers of the abdominal incision. For closure of the abdominal wound we advocate and have used both No. 32 stainless steel wire suture in the fascia and No. 28 wire extraperitoneal retention sutures. Adequate support throughout the entire procedure and postoperatively is of paramount importance. The judicious replacement of whole blood is extremely essential. Correct fluid and electrolyte balance is very important since the return of normal bowel function is delayed and gastrointestinal intubation and suction are used routinely. Drains are advanced daily and removed at the end of 96 hours. In those patients with Chaffin-Pratt suction in operation, irrigation is continued until the return is clear, then the tube is advanced and removed.

A summary of the postoperative data and subsequent complications is contained in Table VI. The period of time necessary for the temperature to return to normal limits is variable and directly related to ancillary complications. At the time of operation, gastrointestinal tubes were inserted in all patients, if this had not been done previously. These were left in place and clamped as bowel activity returned and were removed only when bowel activity had become well-established for over 12 hours. These periods of time are recorded in Table VI. The average time for the cases studied was 4.8 days which compares favorably with the results from other clinics.^{15, 16, 21}

As revealed in Table VI also, this method of surgical management is not without its

complications, both immediate and delayed. These are listed for our 9 cases. Abdominal wound infection and dehiscence occurred as noted in 2 cases. The use of wire fascial and extraperitoneal retention sutures helps to alleviate this problem but does not completely eliminate it. Acute vasomotor collapse with concomitant oliguria occurred once only and required intensive treatment with blood transfusions, steroids, and intravenous vasopressors. Such a clinical picture is suggestive of the generalized "Shwartzman phenomenon" in which the circulating endotoxin from the fulminating infection is the causative agent.²³ Intestinal obstruction occurred as long term complications in 2 cases. Both required exploratory laparotomy for relief of mechanical obstruction secondary to adhesions.

The duration of postoperative hospitalization is listed in column 4 of Table VI. In those cases in which the postoperative course was uncomplicated, the period of total hospitalization was comparable to the figure of

13.5 days given by de Alvarez and Figge¹³ for their cases managed with the conservative regimen. However, as with other forms of operation, when complications arise, the length of hospitalization increases in direct proportion to the seriousness of the pathologic process present.

Summary

A brief discussion of acute pelvic infections and various methods of management has been presented. The extreme importance of recognizing all cases which do not respond to conservative management is emphasized. Such cases are termed "refractory" and require additional definitive surgical therapy in order to prevent the death of the patient.

All admissions to the Gynecology Service of the United States Naval Hospital, San Diego, California, were reviewed for the 3 year period from July, 1956, to June, 1959. A total of 87 admissions for acute pelvic infection were noted and 9 cases "refractory"

Table V. Operative data

Case	Findings at operation	Surgical procedure performed
1. (E. L. B.)	Ruptured right tuboovarian abscess with spillage and generalized peritonitis	En bloc panhysterectomy, bilateral salpingo-oophorectomy, appendectomy
2. (J. S. S.)	Ruptured right tuboovarian abscess with spillage and generalized peritonitis	Excision of right tuboovarian abscess; drainage of area with Chaffin-Pratt tube
3. (C. R. H.)	Numerous pockets of purulent material in abdomen; bleeding from branch of right uterine artery	Ligation of bleeding vessel, lysis of adhesions, irrigation, and drainage*
4. (M. V. E.)	Bilateral tuboovarian abscesses and numerous adhesions	En bloc panhysterectomy and bilateral salpingo-oophorectomy
5. (A. H. G.)	Myomatous uterus and bilateral tuboovarian abscesses with spillage and generalized peritonitis	En bloc panhysterectomy, bilateral salpingo-oophorectomy, and appendectomy
6. (M. A. H.)	Bilateral tuboovarian abscesses with spillage and generalized peritonitis	En bloc panhysterectomy and bilateral salpingo-oophorectomy
7. (P. A. G.)	Bilateral semicollapsed tuboovarian abscesses, numerous localized pockets of purulent material	En bloc panhysterectomy and bilateral salpingo-oophorectomy
8. (M. A. V.)	Ruptured left tuboovarian abscess with spillage and generalized peritonitis	Excision of left tuboovarian abscess and drainage of area with Chaffin-Pratt tube
9. (M. A. V.)	Ruptured right tuboovarian abscess with spillage and generalized peritonitis	En bloc panhysterectomy and bilateral salpingo-oophorectomy

*Peritoneal cavity was irrigated with normal saline in all instances and 1,000,000 units of aqueous penicillin, 0.5 Gm. streptomycin instilled into peritoneal cavity. All pelvis routinely drained through vaginal cuff or cul-de-sac; subfascial drains placed.

Table VI. Postoperative data

Case	Return to normal temperature	Return of bowel function (days)	Complications	Time of discharge (postoperative day)
1. (E. L. B.)	48 hours	4	None	13th
2. (J. S. S.)	96 hours	4	None	8th
3. (C. R. H.)	18 days	6	Abdominal wound infection and breakdown 2 times requiring closure	34th
4. (M. V. E.)	72 hours	3	Intestinal obstruction 31 days postoperatively requiring laparotomy	7th
5. (A. H. G.)	96 hours	5	None	9th
6. (M. A. H.)	6 days	6	Marked hypotension and oliguria 24 hours postoperatively requiring blood, cortisone, and vasopressors	30th
7. (P. A. G.)	96 hours	5	None	12th
8. (A. S. W.)	5 days	5	Intestinal obstruction 83 days postoperatively requiring laparotomy	9th
9. (M. A. V.)	10 days	6	Abdominal wound infection and breakdown requiring closure	23rd

to conservative medical management were studied in detail. The surgical treatment of these 9 "refractory" cases was compared to both conservative management and similar operative treatment by other investigators. The surgical technique, postoperative care, and subsequent complications were presented and discussed in detail.

Conclusions

1. Acute pelvic infections still represent a common gynecologic problem seen, however, more frequently in hospitals caring for indigent patients.

2. Acute pelvic infections in most instances respond to a medical regimen of antibiotics and general supportive measures.

3. A small percentage of acute pelvic infections do not respond to the conservative medical regimen, become "refractory," and require definitive surgical treatment.

4. Surgical intervention in acute pelvic infection should be restricted to those cases which: (a) Show rapid deterioration despite intensive medical management; (b) reveal evidence of ruptured tuboovarian mass or abscess with subsequent acute generalized peritonitis and shock; (c) reveal evidence

of intraperitoneal bleeding secondary to the erosion of a major blood vessel by infection.

5. Surgical management of refractory cases of acute pelvic infection should be as complete as possible with removal of the entire uterus and both adnexa if technically feasible. Good drainage in all cases is considered mandatory.

6. Surgical intervention in the presence of acute fulminating pelvic infection is not without its complications, both immediate and delayed, but is considered to be a warranted risk if carried out as a lifesaving measure.

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Residues of pelvic inflammatory disease and abnormal uterine bleeding

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FOR many years, the problems related to the causation of abnormal bleeding have been of particular interest to us. The exact mechanism of such bleeding has never been satisfactorily explained, and no one knows whether or not the many pathologic conditions which may be found in the pelvis of the woman who is an abnormal bleeder are actually causes or merely coincidental. Certainly, there are many lesions to which time-honored beliefs award a causative role, namely: ovarian tumors, pelvic endometriosis, adenomyosis, pelvic inflammatory disease, and the healed residues of previous pelvic inflammatory disease. In none of these conditions has the mechanism for bleeding actually been proved, although attempts, of a sort, have been made to discover the cause and effect relationship of these lesions to abnormal bleeding. Because we suspected that certain ones of these "causative" lesions might be only coincidental findings, we undertook a study of the general problem of abnormal bleeding, dividing the topic into many parts.

First, it was necessary to list all that is included in the term abnormal uterine bleeding. The following types of bleeding are included under the general heading:

1. An increased amount of bleeding at a menstrual period, as compared with the patient's previous menses. It is felt that such bleeding (menorrhagia or hypermenorrhea),

to be abnormal, must be increased from half again to twice as much as the usual, according to the patient's opinion. This subdivision would obviously include gushing uterine bleeding at the time of menstruation.

2. Prolonged menstrual flow. Realizing that the duration of flow may normally vary a day or two from month to month, it is felt that a menstrual period must continue approximately twice as long as usual to be classified as abnormal for a particular patient.

3. Intermenstrual bleeding. (We attempt to exclude ovulatory bleeding, primarily by history, also by pelvic examination.)

4. Postcoital bleeding which, in all likelihood, indicates the presence of a local lesion, usually on the cervix, to wit: cervicitis, a protruding polyp, or cancer.

5. Shortened intervals in the menstrual cycle. Most women recognize minor variations in their cycle duration, however, those whose intervals are shortened to 21 days or less, are considered to be bleeding abnormally.

6. Postclimacteric bleeding, for any bleeding occurring one year or more after the menopause certainly must be classified as abnormal.

As the first part¹ of our long-range study, we analyzed the clinical histories of 74 consecutive patients from whom non-hormone-producing tumors had been removed and the uteri were still available for observation. Although 15 patients (20 per cent) were bleeding abnormally, 12 patients (four fifths of the abnormal bleeders) had local patho-

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logic conditions which explained the bleeding. Only 3 cases (4 per cent of the total series) could not be explained. As we were doubtful whether our series contained sufficient numbers, we gathered data from the next 80 consecutive patients² with non-hormone-producing ovarian tumors. All conditions were the same for the study. We found only 6 with unexplained abnormal uterine bleeding, and three of these had adenomyosis which we have since come to believe can cause abnormal bleeding. There remained then, only 3 instances (3.7 per cent) of unexplained bleeding in the second study. In combining the results of the two studies, we discovered that 6 out of 154 patients had abnormal uterine bleeding that was not satisfactorily explained by the associated pathologic condition. Consequently, we believe that this unexplained increment was sufficiently low, which excluded non-hormone-producing tumors as a cause of abnormal bleeding.

Our next series³ involved 119 consecutive patients in whom diagnosis of external endometriosis had been confirmed microscopically. Forty of these patients (33.6 per cent) had complained of abnormal bleeding.

Coexisting pathologic conditions appeared to explain the bleeding in 31 of these women, but in 9 (7.5 per cent of the total series) the bleeding was unexplained. Such a low unexplained increment also appeared to exonerate external endometriosis as a cause of abnormal bleeding—in spite of numerous statements to the contrary that appear repeatedly in textbooks and in the current literature.

We then turned our attention to adenomyosis of the uterus.⁴ One hundred and three such cases were thoroughly studied. These also were consecutive cases. Fifty-two of these patients (50 per cent) had been bleeding abnormally. After associated pathologic conditions had been excluded as the cause of bleeding, 27 cases (26 per cent of the total series) were still unexplained. This percentage was much higher than our finding of 7.5 per cent and 4 per cent for the series of external endometriosis cases for the non-hormone-producing ovarian tumors, respectively.

Consequently, we concluded that adenomyosis uteri should be considered to be one of many causes of abnormal uterine bleeding.

The present study was undertaken to discover what role, in the production of abnormal uterine bleeding, healed residues of previous pelvic inflammatory disease play. Unfortunately, it is very difficult to glean much specific information concerning this subject from the literature. Most reports discuss acute pelvic inflammatory disease as an entity and group everything else under the heading of chronic pelvic inflammatory diseases. There are many statements concerning the general subject of uterine bleeding and pelvic inflammatory disease which are of interest. Brewer⁵ notes an association of abnormal bleeding with residues and suggests that "the abnormal uterine bleeding, which is the result of disturbed ovarian function, consists of excessive and prolonged menstrual flow, bleeding too often and in a few instances continuous bleeding." The late Emil Novak⁶ discussed the subject, in general terms, in his textbook stating that "menorrhagia is not uncommon, though rarely excessive, and disturbances in menstrual rhythm are also frequent, generally in the direction of a shortening of the interval." Sometime later, however, while discussing Smiley and Bozeman's paper,⁷ Dr. Novak⁸ voiced doubt that a relationship actually existed between residues and abnormal bleeding. In that paper, Smiley and Bozeman had indicated their belief in the relationship and even suggested a mechanism stating that, "the irregular bleeding frequently encountered results (possibly) from failure of ovulation." Hessel-tine⁹ stated that "pelvic inflammatory disease is fairly frequently associated with excessive or prolonged flow." Textbooks by Crossen and Crossen,¹⁰ Behrman and Gosling,¹¹ and by Taylor¹² suggest the existence of some relationship between chronic pelvic inflammatory disease and abnormal bleeding but no specific studies are described. Young,¹³ in speaking of "long-standing . . . chronic salpingo-oophoritis," stated that "menorrhagia and polymenorrhagia are common." Curtis and Huffman¹⁴ considered the subject

of "chronic pelvic cellulitis" and listed several indications for operative intervention. One of these was "functional bleeding." The cause of such bleeding was attributed to a "disturbance of the ovary (displacement, infection or degeneration) sufficient to interfere with its regulation of menstruation." Lash¹⁵ also felt that "uterine bleeding induced by pelvic inflammatory disease" was an indication for operation after the acute inflammatory phase had subsided. Louw¹⁶ believed that "menorrhagia" was caused by pelvic inflammatory disease. Thus, it was with some confusion that we turned to the material at hand.

Material

One hundred and thirty-four consecutive cases of residues of pelvic inflammatory disease were studied. In order to use undisputable criteria for the evidences of residues of pelvic inflammatory disease, only those cases with a hydrosalpinx were included in our studies. Further, if there was histologic evidence of an active salpingitis, the case was considered to be pelvic inflammatory disease rather than an example of residues. All cases were from the Gynecologic Service of the Chicago Wesley Memorial Hospital. The descriptions of the pathologic conditions were obtained by reviewing the resident-dictated operative reports, the gross and microscopic reports of the hospital pathologists, and, finally, personal examination of both hospital sections and sections made at the Obstetrical-Gynecological Departmental Laboratory at Northwestern University Medical School where all gross specimens were eventually taken. All specimens used in this study included the uterus. These uteri had been opened and examined in the operating room prior to being transported to the General Pathology Laboratory of Wesley. The presence of associated pathologic conditions was determined by the same methods as were utilized in determining the presence of residues of a previous pelvic inflammatory disease.

Complaints presented by these patients with residues were numerous, but also sig-

Table I. Complaints of cases of residues

Abdominal discomfort	76
Abnormal bleeding	67
Tumor	20
Dysmenorrhea	11
Dyspareunia	5
Urinary frequency	4

nificant. These are listed in Table I. Because many patients complained of two or more things, the number of complaints exceeds the number of patients in the series. As was expected, abdominal discomfort headed the list of complaints; in fact, 76 (57 per cent) of the patients complained of pain. Unexpectedly, however, 57 (43 per cent) of the 134 patients complained of abnormal bleeding. Such a high uncorrected percentage of patients with abnormal bleeding came as a distinct surprise to us.

Table II lists the preoperative diagnoses. These would not be expected to be the same as the postoperative diagnoses in each instance and, in fact, neither of the tubal pregnancies diagnosed were found when the abdomens were opened. In reviewing the indications for operation, fibroids and residues, fibroids or residues made up 88 per cent or 118 of the cases as illustrated.

As can be seen in Table III which categorizes the types of abnormal bleeding occurring in the 134 cases, 82 per cent were concerned with an increased flow at menses (47 of 57 cases).

In a search through the tissues for possible causes of abnormal bleeding, many associated pathologic conditions were found. Table IV lists these various types of conditions encountered and records the incidence with which

Table II. Indications for operation

Fibroids and residues	59
Fibroids	34
Residues	25
Ovarian tumors	9
Preinvasive squamous cell carcinoma of cervix	5
Ectopic pregnancy	2
Total	134

Table III. Types of bleeding

Increased flow	39
Increased flow and intermenstrual bleeding	8
Intermenstrual bleeding	6
Postcoital bleeding	3
Decreased interval	1
Total	57

Table IV. Pathologic conditions

No associated pathologic condition	25
Myomas	103
Endometrial polyps	14
Ovarian cystomas	9
Stage 0 squamous cell carcinoma of cervix	7
Adenomyosis uteri	5
External endometriosis	5
Endocervical polyps	4
Invasive squamous cell carcinoma of cervix	1
Brenner tumor	1
Tuberculous endometritis	1
Benign cystic teratoid tumors	2
Cystomas	6

they occurred. It was startling to find that 103, (81 per cent) of the 134 cases had associated fibroids in one part of the uterus or another. Whether or not the high percentage of Negroes in this series (65 per cent) is pertinent, we do not definitely know. What relationship all of these associated conditions bore to the abnormal bleeding was also rather difficult to determine. However, we classified, as possible causes, only lesions that we felt were generally accepted causes of abnormal bleeding and that were definitely demonstrable in each particular case. Such lesions included submucous fibromyomas, endometrial polyps, adenomyosis uteri, invasive squamous cell carcinoma of the cervix, acute cervicitis (contact bleeding), and possibly the injudicious use of hormones. There were 31 instances wherein we believed that the associated pathologic conditions actually caused the abnormal bleeding. The list of lesions and the frequency with which each occurred are recorded in Table V, along with the type of bleeding which they are alleged to have caused. There were 3 types of bleeding,

namely, increased flow, intermenstrual bleeding, and postcoital bleeding. In the increased flow group, 22 of the 25 instances were thought to be caused by submucous fibroids. Another was probably caused by a combination of submucous fibroid and adenomyosis uteri; however, this particular patient complained both of marked increase in amount of flow and of intermenstrual spotting. The only pathologic condition, other than the residues in 5 patients, was endometrial polyps. After much debate, we finally concluded that the polyps could not be ruled out as a cause of the abnormal bleeding. One patient had fibroids and had had abnormal bleeding; she had been treated with radium, and had remained amenorrheic for one year. Thereafter, she received "daily" hormone shots for "many days," then biweekly for several weeks, the last of which was 3 weeks before examination. When seen she had been bleeding off and on for 3 months and on three occasions had bled profusely. It seems quite possible that the endometrium, though not stimulated now, could have been stimulated recently and could have caused bleeding—at least we did not dare exonerate the previous treatment with hormones.

There remained 26 cases where abnormal bleeding was not present, but where no cause seemed obvious. Certainly, there were enough associated conditions present. As indicated in Table VI, 22 of these 26 patients had fibroids. Eleven also had fibroids which were 3 to 4 cm. in diameter or larger, but in no instance was there evidence that these fibroids were submucous. Analysis of the type of bleeding appears in Table VII. Twenty-two of the 26 patients had increased flow, and 6 of these had intermenstrual bleeding as well. The 22 patients with fibroids were not entirely the same patients with increased flow. There were 3 patients without fibroids who had increased bleeding at menses. The 2 patients with endometrial polyps were included in this group because they had hemorrhagic tips. Because 26 instances of abnormal bleeding could not be explained by the same methods that we had used in previous studies, the unexplained increment of 19.4 per cent

should be comparably significant. This is almost twice as great as the percentage which we consider permissible, without pointing an accusing finger at the particular condition as the cause of the bleeding, in this instance, residues of pelvic inflammatory disease.

For the sake of comparison, 36 consecutive cases of tuboovarian abscess and acute salpingitis were reviewed. The uterus was available in each instance. Of the 36 patients, 13 (36.1 per cent) complained of abnormal bleeding. Of these, 7 cases were explained on the basis of submucous fibroids or a submucous fibroid with polyps. There were 2 cases of hemorrhagic endometritis. In the "unexplained" 6 cases, 4 had no associated pathologic condition, while, of the remaining 2, in one there was an intramural fibroid and, in the other, a benign cystic teratoid tumor as well as an intramural fibroid. The types and percentages of abnormal bleeding were similar to those in the residues series. Twelve out of 13 patients complained of increased flow. Three complained of intermenstrual spotting, one also complained of decreased interval, increased flow, and intermenstrual bleeding, while the last one com-

Table V. Explained abnormal bleeding

Type of bleeding	Lesion explaining it	No. of cases
Increased at menses	Submucous fibroid	22
	Adenomyosis and submucous fibroid	$\frac{1}{23}$
Increased at menses and intermenstrual	Multiple endometrial polyps	1
	Postradiation estrogen hormone	$\frac{1}{2}$
Intermenstrual spotting	Endometrial polyps	4
	Invasive squamous cell carcinoma of cervix	$\frac{1}{5}$
Postcoital bleeding	Acute cervicitis	$\frac{1}{1}$
Total		31

Table VI. Pathologic conditions with unexplained bleeding

Fibroids	22
Preinvasive carcinoma of cervix	2
Endometrial polyp	2
Endometriosis	5
Cystoma of ovary	1
Endocervical polyp	1

Table VII. Unexplainable bleeding in residue cases

Increased flow	16
Increased flow plus intermenstrual bleeding	6
Postcoital bleeding	2
Intermenstrual bleeding	1
Decreased interval to 14 days and intermenstrual bleeding	1
Total	26

plained only of spotting between periods. All 6 of those with unexplained cases complained of increased flow, and 2 of intermenstrual spotting. Here, then, is an unexplained increment of 16.7 per cent, quite similar to the 19.6 per cent seen in the residues series—a most interesting parallel.

An interesting sidelight was the low incidence of endometriosis in this series, 6 cases (4.5 per cent). This is significantly below the expected (microscopically confirmed) incidence in our operating rooms (12 per cent).

Summary

One hundred and thirty-four consecutive patients with residues of pelvic inflammatory disease have been thoroughly studied. We found that 57 (42 per cent) of these patients complained of abnormal bleeding. Thirty-one of these cases could be explained by the associated pathologic condition, leaving 26 (19.6 per cent) otherwise unexplained, unless by the residues. The type of bleeding is predominantly one of increased flow.

After careful evaluation of these cases, we are forced to conclude that, in some way, residues of previous pelvic inflammatory disease are a factor in the causation of abnormal uterine bleeding; but the precise mechanism is, for the moment, unclear.

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Regional enteritis simulating pelvic inflammatory disease

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DISEASES of the intestinal tract in women have often been confused with those of the internal genitals. The proximity of both systems makes this possible. Such conditions as malignancy of the rectosigmoid, diverticulitis and diverticulosis of the colon, ulcerative colitis, and appendicitis have at times produced a kind of bizarre symptomatology that has made it difficult to distinguish those diseases from lesions of the uterus, tubes, and ovaries. Consequently a thorough investigation of both tracts is necessary. A complete history, physical examination, and employment of the indicated laboratory procedures should be made before operation is attempted in any gynecologic case, particularly where the findings are equivocal. Even after extensive studies, unsuspected lesions may present themselves at the time of surgical exploration.

This is a report of a patient in whom the preoperative diagnosis was nonspecific inflammatory disease of the left tube and ovary but who at operation was found to have regional enteritis. Although the latter entity is now well recognized and many excellent reports have appeared in the literature since it was first described,^{2, 6, 8, 9, 11, 12, 13} occasionally the findings are so masked as to make the diagnosis obscure. This is particularly true if the patient is seen at the beginning of the disease process. It is most

unlikely that regional enteritis would be mistaken for pelvic inflammatory disease. However, previous investigators report that at times regional enteritis has been hard to distinguish from appendicitis or from benign or malignant tumors of the uterus or ovaries.^{3, 6}

In 1932, Crohn, Ginzburg, and Oppenheimer⁵ assigned the term "regional ileitis" to a complexity of signs and symptoms referable to the lower abdomen and intestinal tract. Prior to their painstaking and exhaustive report, this disease was thought to be of tuberculous origin, a granulomatous tumor of undetermined origin or a condition labeled "pseudocancer." With the presentation of their erudite study, the symptom complex gained the status of a distinct entity, even though a review of the historical aspects made by Pugh emphasizes the belief that the disease has existed for centuries.¹¹ The paper by Crohn, Ginzburg, and Oppenheimer described involvement of the terminal ileum. Subsequently the disease was found to encompass other portions of the intestinal tract, such as the esophagus, stomach, duodenum, jejunum, upper ileum, large segments of the colon, and even the rectosigmoid.⁸ Regardless of the location, there are often abscesses as well as internal, external, and anal fistulas. Despite the propensity of involvement of the terminal ileum, the term "regional enteritis" supplanted the original nomenclature since other portions of the intestinal tract may be included in this entity.¹²

The clinical picture varies with the stage, the duration, and the location of the disease.

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Generally, the patient complains of intermittent abdominal pain and sporadic diarrhea. Upon physical examination an abdominal mass is usually found. These findings may be associated with a slight elevation of temperature and mild anemia. The disease is generally chronic although it may begin as an acute process simulating appendicitis.

The pathological specimen is quite distinctive. It begins as a proliferative process in the interstitial structure of the bowel wall and gradually assumes the characteristics of a scar-forming granulomatous lesion. The etiological factors even after 28 years remain uncertain. Many theories have been advanced; chief among them are infection by the tubercle bacillus, other bacterial infection, virus infestations, allergic phenomena, and trauma. Although the histological and pathological picture of Boeck's sarcoid is similar to regional enteritis, most authorities believe that the two diseases bear little relationship.^{1, 6, 10} As yet no specific cause has been assigned to the latter process. Regional enteritis is said to appear more often in men, the ratio being 3 to 2. It may occur at any age, but 75 per cent of the cases are first recognized when the patient is between the ages of 20 and 40. In a series of 600 at the Mayo Clinic¹² 71 per cent were found in people of northern European extraction and 25 per cent in Jews. According to Crohn³ there is a distinct tendency toward familial involvement.

Although this disorder has occasionally been mistaken for one in the gynecologic tract, there is no particular reference to it in the literature dealing with diseases of women. It is generally agreed that there is little interference with the menstrual function, even in severe cases. Crohn, Yarnis, and Korelitz⁷ in 1956 made an extensive study of 84 cases of regional enteritis in pregnant women. They divided their patients into four groups, and only in those patients where enteritis began during pregnancy was the prognosis poor for mother and infant. When one deals with a suspected case of regional enteritis a definite diagnosis may be difficult

since the onset is often hidden. The unusual features in our case where all of the complaints and signs directed us toward the female genitals make it important to record.

Case report

Mrs. L. G. was first seen at the age of 40 with the complaint of infertility. She had been married for 1½ years and, despite the absence of contraception, she had failed to conceive. The menses began at the age of 12, appeared every 28 days, and lasted from 2 to 3 days. There was no menorrhagia, metrorrhagia, or dysmenorrhea. Soon after her first visit she missed a period and it was thought that she might be pregnant. However, she had a presumed spontaneous abortion, and examination of the curettage specimen was confirmative. The periods resumed their regularity and she was treated expectantly for a year with the hope that a pregnancy might supervene. At the end of that time, because of the infertility, a complete investigation was made of both partners. The husband was found to have no evidence of endocrine, genital, or seminal fluid abnormality. The patient's Fallopian tubes were patent, ovulation was regular, and there was no evidence of endocrine abnormality. Homologous artificial insemination was attempted upon nine occasions. Following the last attempt, the patient began to have severe lower abdominal pain associated with the menses and marked pain in the abdomen between periods. There were no bladder or bowel symptoms. She had a slight temperature elevation. She was treated with antispasmodics, narcotics for pain relief, antibiotics, and bed rest. The pelvic examination revealed bilateral adnexal masses. On the basis of this it was thought that she had pelvic inflammatory disease which had been precipitated by the previous manipulation. Under the instituted regimen the pelvic masses subsided. To complete the recovery, diathermy by the abdominal route and cortisone by mouth were added. The laboratory examination showed no increase in the sedimentation rate; the leukocyte count was 9,550 with 65 per cent polymorphonuclear cells. There was no shift to the left. The hemoglobin level was 116 Gm.; the erythrocyte count was 4.38 million. After a period of 3 weeks the patient was relatively free of discomfort. The mass in the right adnexal region was no longer palpable but the one on the left became better defined. At no time were any abdominal masses felt. During the acute stage of this illness the

patient had spasm and pain in the entire portion of the lower abdomen. When all of the symptoms had subsided a radiographic examination of the lower bowel was made. This failed to demonstrate an extrinsic or intrinsic mass or any disease involving the intestinal tract.

The family, past, and systemic histories gave no additional information. The general somatic physical examination disclosed all findings to be within physiological limits.

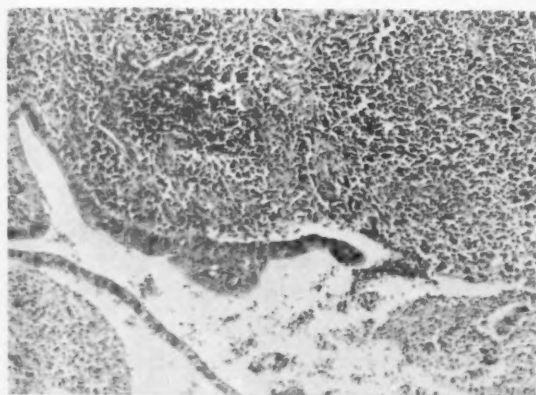


Fig. 1. Photomicrograph of intestinal lesion at the site of perforation.

Because of the persistence of the left adnexal mass, the recurrent bouts of abdominal pain, the nature of the onset of the disease, and the response to cortisone and antibiotic therapy, a diagnosis of left tuboovarian pelvic inflammatory disease was made. This was confirmed by consultation, and exploratory laparotomy was advised.

Under general anesthesia the patient was put in lithotomy position and a pelvic examination was performed. The pelvic mass on the left side was confirmed. It was believed to blend into the uterus and was suspected to be tube and ovary. The preoperative diagnosis was left hydrosalpinx or left ovarian cyst, inflammatory in nature. However, when the abdomen was opened, both tubes and ovaries were normal in appearance and showed no evidence of an inflammatory lesion. The terminal portion of the ileum was found to be adherent to the left uterine cornu. The mass was freed from the uterus and the defect was repaired. The involved portion of the small intestine had perforated but had sealed itself off against the uterine wall. Approximately

24 cm. of the terminal ileum was resected and an end-to-side anastomosis was made between the remaining ileum and the ascending colon.

The pathologist's report of the specimen showed a 24 cm. segment of ileum which had perforated at the mesenteric border. The bowel wall was thickened and hemorrhagic, but there was no evidence of obstruction. The findings were consistent with regional enteritis (Fig. 1).

The postoperative course was complicated by fever and moderate wound infection which responded to antibiotic therapy. The patient made an excellent recovery. Since the operation she has gained weight and has felt well. Except for slight diarrhea there have been no complaints. A radiographic survey of the entire intestinal tract revealed no recurrence of the disease and no evidence of obstruction. To this date, she has failed to become pregnant.

Comment

When dealing with questionable masses in the pelvis, the establishment of an exact diagnosis before operation, if possible, is imperative. If a pathological lesion involving the intestinal tract is suspected or has to be ruled out, the preoperative antibiotic preparation of the bowel is essential for an uncomplicated convalescence. Therefore, equivocal findings should always be surveyed by radiographic, proctoscopic, and sigmoidoscopic examination. Despite these aids in diagnosis there are occasions when such diseases as diverticulitis, diverticulosis, endometriosis of the colon, lymphopathia venereum, carcinoma of the colon and rectosigmoid, and regional enteritis remain obscure until the time of operation.

Our patient had been investigated thoroughly before operation was considered, although a gastrointestinal series had not been done.

The logical diagnosis seemed to be inflammatory disease of the left adnexa inasmuch as there was no previous history of diarrhea, abdominal pain, or fever. The signs and symptoms were precipitated by the last artificial insemination. The persistent mass in the left side of the pelvis appeared to be attached to the uterus; it was not visualized at the time of the barium enema.

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Trichomonas vaginalis infection

Critical evaluation of 3 locally applied medications

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TRICHOMONAS VAGINALIS vaginitis is one of the most common conditions that present-day gynecologists are called upon to diagnose and treat. Many medications have been employed in the treatment of this infection, varying from plant germicides and medicinal herbs to multiple combinations of complicated chemical compounds, and each passing year finds the literature replete with accounts and advertisements of newer and better drugs complete with glowing testimonies of high percentages of cures.^{2, 4, 6, 8, 9, 14-19} It must be obvious, however, from both the number and the variety of advocated medications, that this is a difficult, if not impossible, organism to eradicate from its natural habitat.¹

The present study was initiated to test the hypothesis that a locally applied estrogenic cream (Compound B),* although not a trichomonacidal compound, might restore the normal physiology, re-establish the normal bacterial flora, and permit the host-parasite defense mechanism to function normally and thus eradicate the trichomonads from the vagina. Second, 2-acetyl-amino-5-nitro-

thiazole* (50 mg. per applicatorful) was added to incorporate the known trichomonacidal features of this compound to the estrogenic cream (Compound A). At the beginning of this investigation, a third local medication, the pure base of the cream without added estrogens or other compounds, was employed (Compound C). The investigation thus originated as a triple-blind study; but as it progressed Compound C was discontinued and the remainder of the cases were treated with either of the first two compounds.

The 3 criteria for inclusion in this study were: (1) complaints of a vaginal discharge, vulvovaginal irritation, burning, and pruritus, dyspareunia, or dysuria either alone or in combination,¹⁷ (2) a positive hanging-drop, wet-smear preparation, and (3) a positive culture. A total of 50 patients were thus included in this series. This is not a series of 50 consecutive patients who presented themselves to the gynecologic clinic of the Woman's Clinic of the New York Hospital, but of 50 patients who met all or some of the 3 criteria mentioned above. Since the general incidence of *Trichomonas vaginalis* in women of all age groups has been reported to be between 20 and 25 per cent,³ it is obvious that many more of the women who attended the clinic during the year when this study was in process may have harbored this organism, but are not included in this study.

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**Dienestrol cream, furnished by Ortho Pharmaceutical Corporation, Raritan, New Jersey.*

**Tritheon, furnished by Ortho Pharmaceutical Corporation, Raritan, New Jersey.*

Table I. Plan of therapy for *Trichomonas vaginalis*

Plan No.	Duration of treatment (weeks)	No. of patients
IA	2	6
IB	4	21
IIA	3	4
IIB	6	19
Total		50

Table II. Results of investigation of patients who had cultures

Medication	Cultures	
	Positive	Negative
Compound A	16	4*
Compound B	19	2†
Compound C	9	0
Total	44	6

*Two of these patients used the medication less than a week before cultures.

†Both of these patients used the medication less than a week before cultures.

Table III. Results of investigation in patients with wet smears

Medication	Wet smears	
	Positive	Negative
Compound A	12	8*
Compound B	17	4†
Compound C	8	1‡
Total	37	13

*Four of these patients had positive cultures. Two had negative cultures but had used the medication the day of examination. Two others had "culture cures."

†Three of these patients had positive cultures. One had a negative culture, but had used the medication the day of examination.

‡Positive culture.

The criterion for cure was strictly a negative culture. We did not consider symptomatic relief or the disappearance of the flagellate from hanging-drop smears as evidence of cure. Almost all of the recent literature on this subject has emphasized the superiority of the culture method over the wet smears.^{1, 3, 5, 7-13, 17, 20}

Plan of therapy

A special vaginitis clinic was established, and one of us (C. J. C.) interviewed and treated each patient, reviewed each hanging drop, and cultured and interpreted each preparation. In the original plan (IA), the patients were given sufficient quantity of medication (supplied in identically unmarked tubes with the contents unknown to both the patients and investigators) with disposable applicators for a period of 2 weeks of daily therapy. They were then requested to discontinue all medications for 1 week and return to the clinic where repeat hanging-drop smears and cultures were obtained. Six patients were included in this plan (Table I). The second plan (IB) included a second 2 week course of therapy followed by a week without medication. Twenty-one patients are included in this plan (Table I). In the third plan (IIA), the patients had an initial 3 week course of therapy followed by a week with no treatment. Four patients are included in this plan (Table I). The fourth plan (IIB) included a second course of 3 weeks' duration followed by a week without treatment. Nineteen patients are included in this plan (Table I). The therapy was to be used throughout the menstrual period (should it occur), and the patients were requested to abstain from intercourse or the husbands asked to use a condom during the weeks of the various plans. If these requirements were not met the patients were not included in the study group.

Diagnosis

Clinical. Forty-eight of the patients had the typical yellowish frothy vaginal discharge with or without signs and symptoms when seen for their original visit. One patient had a complaint of dyspareunia and no discharge, but a positive hanging drop and culture were obtained from the vagina. One patient had complaints of a vulvar irritation, burning, and pruritus, and no discharge, but also had a positive hanging drop and culture.

Laboratory.

1. *Hanging drop.* All 50 patients had a positive hanging-drop smear. These were

prepared in the routine fashion employing warmed normal saline as the diluent and a covered depressed slide viewed under both low and high power with a conventional monocular microscope.

2. *Culture*. Forty-nine of these patients had a positive culture on the initial examination. One patient had a positive hanging-drop smear but negative culture on the initial examination, however, she had subsequent positive cultures. We employed a trypticase serum medium containing trypticase, cysteine, maltose, Difco agar, and human serum all adjusted to a pH of 6.0. Penicillin (25 units per cubic centimeter) and streptomycin (1 mg. per milliliter) were added. This medium was inoculated and incubated within a short time of the procurement of the culture at 37° C. and checked daily by the hanging-drop technique until either a positive result was obtained or for a period of 7 days if there was no growth. No tube was considered negative until the 7 days had passed.^{9, 17} All of the patients also had cultures for *Candida albicans*, with the use of Nickerson's

medium.¹⁸ A Nickerson slant was streaked and incubated at 37° C. up to 7 days and examined for the presence of the characteristic very dark brown or black colonies. Forty-three of the patients had only *Trichomonas* infection and 7 had a mixed infection of both *Trichomonas* and *Monilia*.

Results

Cures. We employed a rigid, unwavering criterion for a cure; i.e., a negative culture after all therapy had been discontinued for 1 week. By this criterion, only 2 of the 50 patients were cured (Table II). Six patients had negative cultures, but 4 of the 6 had used the medication less than a week before the cultures were obtained and, therefore, were not considered as being cured. Both of the "cures" were in patients who had used the estrogenic cream with the added Tritheon (Compound A). One of these patients used the compound for 4 weeks (Plan IB); and the second used the material for 6 weeks (Plan IIB).

Wet smears. The use of the estrogenic

Table IV. Results of investigation of patients with discharge

	<i>Eradicated</i>	<i>Improved</i>	<i>Unchanged</i>	<i>Worsened</i>	<i>Total</i>
Compound A	9	5	5	0	19
Compound B	8	4	9	0	21
Compound C	3	1	4	0	8
Total	20	10	18	0	48

Table V. Results of investigation of patients with vulvovaginal irritation

	<i>Eradicated</i>	<i>Improved</i>	<i>Unchanged</i>	<i>Worsened</i>	<i>Total</i>
Compound A	4	1	1	4	10
Compound B	7	0	2	1	10
Compound C	2	2	1	0	5
Total	13	3	4	5	25

Table VI. Results of investigation of patients with burning and pruritus

	<i>Eradicated</i>	<i>Improved</i>	<i>Unchanged</i>	<i>Worsened</i>	<i>Total</i>
Compound A	7	2	3	2	14
Compound B	6	1	3	4	14
Compound C	3	3	1	0	7
Total	16	6	7	6	35

cream (Compound B) resulted in the disappearance of the flagellate from the wet smear in 4 of the 21 patients. However, 3 of these had positive cultures obtained at the same time as the negative smears and the last had used the medication the day of the examination (Table III).

The use of the estrogenic cream with the added trichomonacidal agent (Compound A) resulted in the disappearance of the trichomonads from the wet smear in 8 of 20 patients. There were 2 of these patients who were also "culture cures." The others either used the medication the day of examination or had positive cultures.

Symptomatic relief. A detailed analysis of each preparation and plan of therapy has been made for each subjective symptom of discharge, irritation, burning and pruritus, dyspareunia, and dysuria. It was apparent that prolonging the course of therapy did not increase the percentage of cures. In fact, it appeared to make the symptoms worse in 13 patients. Therefore, for clarity and brevity, we have combined all the original 4 plans of therapy.

Of the 48 patients with the initial complaint of a vaginal discharge, 20 or 41.6 per cent were completely relieved of their symptoms, 10 or 20.8 per cent were improved, and 18 or 37.5 per cent were unchanged (Table IV). It is evident, however, that there was no difference in the percentage of symptomatic relief regardless of the medication employed.

Of the 25 patients with an initial complaint of vulvovaginal irritation, 13 or 52 per cent became symptom free, 3 or 12.0 per cent were improved, 4 or 16 per cent were unchanged, and 5 or 20 per cent were made worse. Again it is evident that there was no difference in the percentage of patients relieved of their symptoms regardless of the medication employed. In fact 4 out of the 5 patients who used the pure base of the vaginal cream alone were relieved or improved (Table V).

Of the 35 patients with an initial complaint of burning and pruritus, 16 or 45.7 per cent were relieved, 6 or 17.1 per cent

were improved, 7 or 20 per cent were unchanged, and 6 or 17.1 per cent were made worse. There is no difference in the medications used and it would actually appear that the use of the vaginal cream alone relieved more patients of this symptom than either of the medicated creams (Table VI).

Of the 28 patients with the initial complaint of dyspareunia, 14 or 50 per cent were symptom free, 11 or 39.3 per cent were unchanged, and 3 or 10.7 per cent were made worse. Again there is no difference in the control of symptoms among the 3 compounds employed (Table VII).

Of the 16 patients with the initial complaint of dysuria, 13 or 81.2 per cent were totally relieved of their symptoms, 2 or 12.5 per cent were unchanged, and 1 or 6.2 per cent were made worse. One might feel at first that the estrogenic cream with the added trichomonacidal agent was best in relief of this symptom, but it is evident that just as many patients were relieved with the use of the base cream alone (Table VIII).

Comment

In the face of the multitude of articles published each year attesting the superiority of one new drug or treatment over another, it seemed worthwhile to record a negative report on a well-controlled series of patients with proved *T. vaginalis* vaginitis.

It is evident that local estrogenic cream alone had no action in this series. The addition of an agent which has been reported as having marked trichomonacidal activity to the estrogenic cream did not in any way increase the percentage of culture cures or symptomatic relief of symptoms.

We feel that strict criteria must be met when reporting on the effectiveness of any trichomonacidal agent. These are (1) using only negative cultures as indicative of cures, and (2) allowing at least a week without medication prior to the evaluation of treatment. If reports use the hanging-drop wet smears as a criterion of cure instead of culture, the percentages of "cures" will be much higher than those which actually exist. If symptomatic relief is used as the criterion

Table VII. Results of investigation of patients with dyspareunia

	<i>Eradicated</i>	<i>Improved</i>	<i>Unchanged</i>	<i>Worsened</i>	<i>Total</i>
Compound A	5	0	4	0	9
Compound B	3	0	6	1	10
Compound C	6	0	1	2	9
Total	14	0	11	3	28

Table VIII. Results of investigation of patients with dysuria

	<i>Eradicated</i>	<i>Improved</i>	<i>Unchanged</i>	<i>Worsened</i>	<i>Total</i>
Compound A	5	0	0	0	5
Compound B	5	0	2	1	8
Compound C	3	0	0	0	3
Total	13	0	2	1	16

of cure, a false picture of the true value of the medication could be inferred. Slightly over half of the patients in this series were "cured" of their varying complaints and an additional 17 per cent were improved. However, an equal percentage were made worse and another 25 per cent were unchanged. Of even greater significance, however, is the fact that there was no difference in either culture cures, disappearance of the flagellates from wet smears, or relief of subjective symptoms among any of the preparations.

Summary and conclusions

1. A study employing a local vaginal cream with added estrogens, the estrogenic cream with added 2-acetyl-amino-5-nitrothiazole, and the base of the vaginal cream with no additives was carried out at the Woman's Clinic of the New York Hospital with 50 patients using 4 different plans of therapy.

2. The criteria for inclusion were (1) subjective complaints of discharge, vulvovaginal irritation, dyspareunia, and dysuria; (2) positive hanging-drop smears, and (3) positive cultures.

3. The criterion for cures was negative cultures.

4. The different plans of therapy varied from 2 to 6 weeks with 6 patients in the first plan, 21 in the second, 4 in the third, and 19 in the fourth for a total of 50 patients.

5. Forty-eight of the patients complained of a vaginal discharge on the initial visit, 25 of vulvovaginal irritation, 35 of burning and pruritus, 28 of dyspareunia, and 16 of dysuria.

6. All 50 patients had positive hanging-drop wet smears on the original examination. Forty-nine had positive cultures. One patient had a positive hanging-drop and negative culture on the original examination, but had subsequent positive cultures.

7. Only 2 of the 50 patients had successful "culture cures." Four others had negative cultures, but had used the medications less than a week prior to the cultures and therefore were not considered cured.

8. The hanging-drop preparations became negative in 4 of the 21 patients treated with the estrogenic cream. However, 3 had positive cultures at the same time. The hanging drop became negative in 8 out of the 20 patients treated with the estrogenic cream plus Tritheon. However, 6 either had positive cultures or used the medication the day of the culture.

9. A detailed analysis of the symptomatic effects of each medication is included. There was no difference in the percentages of symptomatic relief of any of the presenting symptoms among the 3 preparations employed.

10. It was evident that the local estrogenic cream had no effect as an antitrichomonas

agent. It was capable of relieving or improving the subjective symptoms, but to no greater extent than either of the other medications. This was likewise true of the estrogenic cream with the added Tritheon and, in fact, of the pure base of the vaginal cream.

11. At the present time there are many

preparations which are capable of relieving the symptoms of *T. vaginalis* vaginitis; some temporarily cause the disappearance of the trichomonads on wet-smear examination and some are trichomonacidal in vivo. There do not appear to be any which will consistently "culture cure" the patient.

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Trichomonas vaginitis in depressed women

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WHILE most women who develop *Trichomonas vaginalis* vaginitis have recurrences, either early or late, the disease is readily relieved by local treatment in the vast majority. However, there is a "hard core" of "refractory" cases that makes up about 10 per cent of the total and, no matter what local measures are recommended, the disease persists in this group for months or even years, during which time the patient continues with the original doctor, or makes the rounds from one doctor to another, confused as to why she cannot be cured. Several years ago Moore and Simpson¹ reported on the emotional component of *Trichomonas* vaginitis, which they regarded as a psychogynecologic disorder, resulting from changes in vaginal physiology subsequent to emotional stress. In their observation any type of stressful situation could initiate the vaginitis, which they advised managing with a minimum of local therapy in order to avoid vaginal "fixation." The goal of treatment, in their view, was helping the patient with her fundamental emotional problem, which occasionally required referral for formal psychotherapy.

The distribution of *Trichomonas* vaginitis in 4 different social groups was recently reported on by Buxton and others² who found these striking contrasts: While there was not a single case among 157 undergraduate students in a women's college, and while the incidence of infestation was 6.3 per cent in a group of 575 routine obstetric and/or gynecologic patients, there was an incidence

of 15 per cent among 715 inmates of two state mental institutions, while a group of 221 women in a state prison showed an incidence of 70 per cent. In discussing the epidemiologic facts cited above, the authors hypothesized such variables as socioeconomic factors, personal hygiene, and so on.

The thesis of the present paper is the proposition that the common denominator in women with "refractory" trichomonas is depression. This conclusion, like the knowledge of any psychiatric syndrome, has been derived from three sources: the history, as obtained from the patient herself; reports about the patient, as obtained from the referring physician, a relative, friend, employer, or other close contact; and the findings on examination. The syndrome of depression with associated intractable *Trichomonas* vaginitis that lasted for a year or longer was observed in 13 out of a total group of 125 women who were observed for symptomatic vaginal trichomoniasis. The characteristic feature of the vaginitis in this hard core of 13 women was the fact that it persisted unabated despite any number of local therapies to which the average patient readily responded, notwithstanding the expected incidence of recurrences, both early and late. Symptomatic and clinically obvious vaginitis* continued refractory to local measures as long as the underlying depression lasted.

*The mere presence of trichomonads in the vaginal secretion does not justify the diagnosis of *Trichomonas* vaginitis, for the protozoan has been identified in 13 per cent of some 84,000 vaginal cytology specimens reviewed at Presbyterian Medical Center (formerly Stanford Hospital), San Francisco. It is noteworthy that in most of the 13 per cent in which trichomonads were found by the cytologists, the referring physicians indicated no suspicion of trichomoniasis.³

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It is not the purpose of this paper to review the classical symptoms and signs of depression which are well known to all physicians. Suffice it to say, the 13 patients herein discussed all evidenced mood or affect depression, expressed by the statement of feeling depressed, dejected, hopeless, or melancholy, and these feelings were verbalized by such terms as being "blue," "unhappy," "low in spirits," "no ambition," "glum," and so on. Depression in the cognitive parameter was as constant a feature of the syndrome as depression of affect, and this was expressed (both by patients and friends or family) as a loss of interest in life and the incapacity to enjoy such activities as reading, sports, travel, entertainment, conversation with cherished friends, and so on. Most patients were able to verbalize the great effort it took to carry out the demands of their ordinary employment, and such routine household activities as shopping, planning meals, keeping the house in order, balancing the check book, etc. Patients who had been avid readers before their illness admitted loss of interest in reading and even inability to keep up with current events through newspapers, radio, and television.

Motor depression was shown in the often troubled or plaintive facial expression, slowness of gait, relaxed posture or stance, and the findings on pelvic examination. Nine times out of 10 pelvic examination of any one of the 13 patients with refractory trichomoniasis showed gaping of the introitus (even in nulliparas), hypotonicity of the levator ani muscles, and a low-lying cervix, suggestive of early descensus. A scybalum was usually noted in the rectal ampulla.*

Of the 13 patients with intractable trichomoniasis as a cardinal expression of their depressive illness, 4 have been selected to illustrate the syndrome under discussion. These vignettes are prototypical of the group.

*The findings on pelvic examination, in the presence or absence of vaginal trichomoniasis, are so consistently present in depressed patients as to suggest the diagnosis of depression to the examining physician.

Case reports

Case 1. Miss A had a "Puritanical upbringing" on a farm in the Midwest. At the age of 23 she went overseas as a civilian employee for a military branch of the Federal Government. Despite many "dates" she remained a virgin until she decided to "give in" to a married officer whom she described as "irresponsible, immature, and unloving." During her first intercourse she "knew" she would become pregnant, and wanted to be, "because that's all men want of me, anyhow!" At the time of her second missed period, she became very depressed, and it was then that *Trichomonas vaginitis* was first diagnosed. It persisted throughout the pregnancy and 2 years thereafter. She states that she still feels "guilty about having given the child out for adoption, although it was the only sensible thing to have done, under the circumstances." She continues depressed, and regards the vaginitis as "something I'll probably always have." She refuses psychotherapy.

Case 2. Mrs. B got married at the age of 20 to an "alcoholic husband," who worked erratically and whom she supported with minimal resentment for 18 years, until "he became interested in another woman." Intractable trichomoniasis began 3 months after the husband's first peccadillo. The vaginitis has persisted during the last 18 months, during which time she has undergone abdominal hysterectomy (for fibroids), has gained 30 pounds in weight ("I have a craving for sweets"), and the husband has married the "other woman," even before his divorce has become final. Mrs. B remarked querulously, "I don't know what he sees in her—she's even fatter than I am, and 10 years older." Mrs. B continues depressed, and preoccupied with the notion that "things might have been better if we had been able to have had a child." She currently is under the care of an internist for duodenal ulcer.

Case 3. Miss C was 41 years of age when she was first seen because of spotting between periods. The referring psychoanalyst described this obese secretary as a "depressed, alcoholic woman, whose alcoholism had brought her into therapy." During the 2 years of psychotherapy the patient's family doctor had treated her at frequent intervals for *Trichomonas vaginitis*, which was "never relieved by anything." Abdominal hysterectomy (with preservation of ovaries) was carried out for carcinoma in situ of the cervix, following which the patient became more and more depressed. Three months after operation she was

hospitalized in a state institution because of "psychotic depression," for which electroconvulsive therapy was given. Six months later she was dismissed "improved," but still depressed and still with florid vaginal trichomoniasis.

Case 4. Miss D, a 43-year-old executive secretary, was referred by a chest physician for treatment of *Trichomonas* vaginitis, which had developed concomitantly with recurrence of "old" pulmonary tuberculosis, for which she was currently receiving antibiotics and (weekly) pneumoperitoneum. During the 18 months of anti-tuberculosis therapy Miss D continued depressed, hostile, vindictive, and often asked, "Why did this have to happen to me?" Two months after the tuberculosis had cleared, she became pleasant, cheerful, interested in sports, former friends, etc., and simultaneously got over the vaginitis, which had been refractory during the 18 months she was depressed and under active treatment for recurrent tuberculosis. (She recalled that when she first had tuberculosis, at the age of 20 and for 2 years, she then, too, was "blue" and "dependent," and had a "persistent discharge.")

Theoretical considerations

The correlation of the vaginal flora (*Döderlein bacillus*) with health and disease has been known since the classical studies of Schröder⁴ in 1921. His Grade I flora, as is well known, consists of *Döderlein bacillus* only, while Grade II contains *Döderlein bacillus* plus other organisms; most instances of infectious vaginitis are in Grade III, being made up entirely of organisms other than *Döderlein*. More recently others⁵ have correlated Schröder's Grades I, II, and III with vaginal pH, which ranges between 3.9 and 5.0 in normal women, i.e., Grade I flora, 4.6 and 5.5 in Grade II, and 5.1 and 6.0 in Grade III. In health the metabolism of mucosal glycogen provides a glucose-lactic acid medium (pH 4 to 5) which is favorable to the growth of *Döderlein bacillus* and inimical to pathogenic organisms. Vaginal acidity thus plays a crucial role in the self-sterilizing capacity of the vaginal surface.

In his bacteria-free culture studies of *Trichomonas vaginalis* Johnson⁶ found that the protozoan enjoys maximal growth between pH 5.5 and 6.0, while it diminishes below pH 5.0 and above pH 7.55, and these

findings were recently confirmed in an independent investigation by Suzuki.⁷ While any number of factors, such as estrogen deficiency (and diminished mucosal glycogen content), trauma, chemical irritants, and so on, are apparently capable of shifting the vaginal buffer system to the alkaline side, favorable to the growth of *Trichomonas vaginalis*, in the vast majority of patients appropriate local treatment will re-establish a normal vaginal pH of approximately 4.0, with a corresponding reversal of the vaginal flora from Grade III to Grade I. One cannot but speculate on the possible role of psychochemistry as a factor in the chronicity of vaginal alkalization which is a constant finding in women with "refractory" *Trichomonas* vaginitis. The vaginal alkalinity is analogous perhaps to the hyperacidity that precedes and accompanies duodenal ulceration.

Therapeutic implications

The physician can be of maximal help to the depressed woman who consults him because of chronic *Trichomonas* vaginitis, it seems to me, if he will de-emphasize the vaginitis, and devote his efforts instead to trying to understand the patient in her social context. Months of repeated pelvic examinations and sundry local treatments, in my observation, all too commonly not only result in a vaginal "fixation," but often end up in a *folie à deux* between the conscientious physician (bent on "attacking" the vaginitis) and the depressed woman. It is not difficult to appreciate how such a patient can (unconsciously) displace anxieties, phobias, and guilt to the "dirty" vagina. Such a physician-patient relationship will often amount to an iatrogenic prolongation of the patient's fundamental illness (depression), instead of being therapeutic. Conditioning the patient to "compulsive" douching and painful local treatments that bring about temporary relief by the clinical production of a superficial slough can only be decried. Such measures only succeed in channeling guilt to the reproductive organs, thus aggravating the underlying depressive illness which invariably has a significant parameter of guilt.

While the doctor's major role should consist in providing support, reassurance, and respect, and while he should alleviate the fear and threat that usually go along with chronic vaginitis, and while he should help the patient by improved insight and self-understanding, there is no reason for his withholding local medicaments directed toward the patient's comfort and the suppression of the infestation. Moreover, there will be times when he will prescribe appropriate psychoactive agents, urge referral for formal psychotherapy, and so on. In any event, the patient's best interests will be served if the maxim *primum non nocere* is always kept in mind in the management of these patients whose persistent vaginitis is merely a shadow or expression of their fundamental illness—depression.

Conclusion

Trichomonas vaginitis of a chronic refractory nature may be the presenting com-

plaint of women whose fundamental illness is depression. About 10 per cent of cases of trichomoniasis seen by doctors fall into this "hard core," which do not respond to the usual local treatments. The vaginitis in these women goes along *pari passu* with the depression and clears only when the depressive episode is over. It is important in these instances to de-emphasize the vaginitis, avoid the tendency to a vaginal fixation, and direct one's attention to a better understanding of the patient in the social context (the external field forces) in which the depression evolved.

We wish to express our appreciation to Dr. Norman Reider for his suggestions which were most helpful in the preparation of this article.

Addendum. In a recent publication from Canada the author noted that emotional disturbances associated with *Trichomonas* vaginitis were apparent in 80 per cent of his series of 92 cases observed in the course of a 4 year study.⁸

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Nongonococcal vulvovaginitis

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FOR over a century, physicians have been searching for the cause of the irritating and offensive disease, nongonococcal vulvovaginitis. Before Neisser's discovery of the gonococcus in 1879, Donné¹ in 1836 described and named a protozoan, *Trichomonas vaginalis*, and suggested that it was a causative agent of vaginitis although at the time he considered it to be associated with gonorrhea. Mycotic infections were first described by Döderlein² in 1892, and it was not until 1955 that Gardner and Dukes³ published their work describing the bacterium *Hemophilus vaginalis* as a specific cause of vaginitis.

Pathology

Prior to puberty, the vaginal mucosal cells contain little or no glycogen, but under the influence of estrogens the vaginal epithelium develops a considerable amount of glycogen, with lactobacilli becoming predominant in the vaginal flora and a resultant acid pH of 4 to 4.5.

Keratinization and desquamation of both vaginal and cervical epithelium may show variations from such causes as intercourse, baths, douches, medications, and different types of infection.

When infection with trichomonads occurs, an increased number of cornified cells of the superficial squamous type is found in the stained vaginal smear, some of them showing irregular outlines and covered with gray mucus. The cytoplasm may be dense and intensely acidophilic. In well-preserved

cells, the nuclei are pinkish and only lightly stained. Parabasal cells with pronounced vacuolation of the cytoplasm may be prominent. In some instances, the nuclei of exfoliated cells are enlarged, irregular in form, and hyperchromatic; these changes, when pronounced, may lead to a false diagnosis of malignancy. Extreme cytologic aberrations are rare in the vagina infected with trichomonads, and most smears show only minor morphologic changes. Usually, the pH is high and there is a rich growth of cocci.

In 1894, Krönig⁴ conducted a series of interesting experiments in pregnant women to determine the bactericidal action of the vaginal secretion. Cultures of *Pseudomonas aeruginosa* were introduced into the vagina and, in all cases, they were destroyed in an average of 20 hours. In his observations, the bacterial destruction occurred most rapidly when the vaginal secretion contained Döderlein's long, nonpathogenic bacilli. This investigator concluded that the vagina becomes aseptic within 2 or 3 days after a foreign material is introduced, and that antiseptic douches weaken or destroy the natural antiseptic action of the vaginal secretion. However, he noted that the gonococcus and *Bacillus aerogenes capsulatus* are very resistant to this natural antiseptic action. In 1887, Döderlein⁵ opposed the popular teaching that prophylactic antiseptic douches were of value in the treatment of vaginitis.

Pathogenesis

In general, nongonococcal vaginitis is usually caused by 1 or more of 3 organisms: *T. vaginalis*, *Candida* species (Monilia), and *H. vaginalis*.

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When invasion of the vagina by any of these 3 agents occurs, the flora almost invariably changes, becoming deficient in lactobacilli. As a result, the desquamated mucosa contains less glycogen and the normally acid pH becomes alkaline.

Trichomonas vaginitis

In 1940, Trussell⁶ succeeded in culturing bacteria-free *T. vaginalis*. This parasite possesses four flagella and an undulating membrane which contains a primary and a secondary filament. In wet smears only very active motility can be observed, whereas in stained smears the flagella and filaments are visible. Trussell was unable to discover evidence of encystment in the strain used.

Biopsies of a vagina infected with *T. vaginalis* show that the surface of the mucosa is spotted with coagulated material, in which trichomonads, leukocytes, and erythrocytes are commonly found. The subepithelial layer contains areas of intense infiltration extending as far as the basal membrane, with occasional necrotic foci. In this connection, Trussell states that there is no reason to deny that bacteria play an important part in the production of the final disease picture.

The increased leukocyte content of vaginal discharge containing trichomonads has been attributed by some investigators to associated bacteria, and they point out that, generally, protozoa are not pyogenic.

The claim by Donn  ⁷ in 1837 that trichomonads cannot possibly live in the cervix has been definitely accepted. However, Bartholin's and Skene's glands can harbor *T. vaginalis*. Attributed sources of infection by this protozoan are: male consorts, birth of a female child from an infected mother, douche nozzles, toilet seats, towels, and instruments. It is very doubtful whether intestinal infection with *Trichomonas hominis* could be a cause of vaginitis.

Monilial vaginitis

Monilial vulvovaginitis is seen with increasing frequency. Pregnancy and diabetes have been considered predisposing factors, probably because of the excessive glycogen

or glucose in the vaginal tissues. Since the introduction of antibiotics, fungal diseases have become increasingly common. Moniliasis, caused mainly by *Candida albicans*, is an acute or chronic infection in which the fungus may injure the vulva, vagina, and perianal region.

The infection in the vagina frequently appears as a "cracker-crumble" discharge which on removal leaves an inflamed surface. It is often accompanied by severe pruritus vulvae. Occasionally, a purely monilial infection may be found in a normally acidic vagina.

Bacterial vaginitis

A newly defined specific vaginal infection, previously classified as nonspecific vaginitis, was discovered by Gardner and Dukes⁸ and the name assigned to the isolated bacillus was *H. vaginalis*. The four steps of Koch's postulates were carried out and the bacterium proved to be the cause of vaginitis. *H. vaginalis* has also been cultured from the male urethra.

Symptoms

Regardless of the cause, vulvovaginitis is accompanied by discharge, pruritus, irritation or soreness, and malodor. These symptoms vary with each of the 3 mentioned causes, as shown in Table I.

Diagnosis

The causative factor of vulvovaginitis can be differentiated by a careful clinical history supplemented by physical examination and more or less simple laboratory procedures. It is essential that the patient abstain from douches or coitus for one or more weeks before microscopy examination or cultures are made. It should be further noted that the finding of trichomonads is not definite proof that this is the only organism producing the disease. A complete examination of the vulva, vagina, and cervix must be made with a nonlubricated speculum, and the color and odor of the discharge should be noted.

A successful attempt was made to de-

Table I

Symptom	Trichomonal	Monilial	Bacterial
Discharge	Yellow to greenish	White, chunky, "cracker-crumb" type	Scant to moderate
Vulval excoriation	Marked	Moderate maceration	Slight redness
Vagina and cervix	"Strawberry" spots	Pink to red with white plaques	Slight redness
Odor	Very foul	Vinegar-like	Very disagreeable
pH	Alkaline	Acid or alkaline	Alkaline

velop a method in which a reliable system of diagnosis could be performed in the office. Many years ago the comparison of results between the office microscopy and cultural proof was very disappointing until it was realized that in some way all three pathogens seemed to adhere to the cotton end of the applicator and also the products of the posterior vaginal pool were full of extraneous material. Hence, the wood end of the applicator was then used with markedly improved results, with the exception of smears taken for detection of *H. vaginalis*, in which clue cells were sought; this was solved by gently scraping the anterior surface of the upper cervical lip. A much better specimen was obtained by using an opened paper clip in the same manner, the small end for urethral smears and the large for the cervix or vagina (Fig. 1). The clip was imbedded in a plastic tube, so that a specimen from either the anterior cervix or the urethra could be obtained with fairly vigorous pressure. The material obtained was then transferred to a drop of saline on a glass slide and immediately examined for *T. vaginalis*, *H. vaginalis*, or other bacteria and fungi. Comparison of our results with cultures was more than 95 per cent positive.

A simplified office method for differential diagnosis is as follows:

1. *T. vaginalis* (wet slide): a drop of normal saline solution on the slide, spreading of a small quantity of vaginal or urethral secretion obtained with the paper clip loop into the drop, placement of the cover slip, and microscopy examination with both low- and high-power oculars.

2. Monilia: can usually be observed on a wet slide or by adding potassium hydroxide

to a dry slide and staining it with cotton blue.

3. Bacteria: observation of "clue cells," as described by Gardner and Dukes, on a wet slide. Gram-stained slide: small gram-negative pleomorphic bacilli frequently forming solid fields outside the cellular elements.

4. Cultures for both Monilia and *H. vaginalis* may be done.

In this study, 177 cases of vulvovaginitis were diagnosed by the method of wet slides, Gram's stain, and cultures, as well as by the clinical manifestations of *T. vaginalis*, monilial, and bacterial infections. In 20 of these cases (11 per cent), a combination of causative agents was found. Laboratory results were as follows:

Types of infections

<i>T. vaginalis</i>	81 (41%)
<i>C. albicans</i>	48 (24%)
<i>H. vaginalis</i>	68 (35%)
	197

Mixed infections included in above series

Trichomonads and Monilia	3
Trichomonads and bacteria	11
Monilia and bacteria	4
Trichomonads, Monilia, and bacteria	2
	20

T. vaginalis appeared in less than 50 per cent of the total number of cases. In mixed infections, this organism was found more often than any of the two other invaders.

Treatment

Because vulvovaginitis is associated with a variety of microorganisms, the ideal therapy would be a preparation which could destroy all 3 important invaders, and at the same time assist in restoring a physiologically normal vagina.

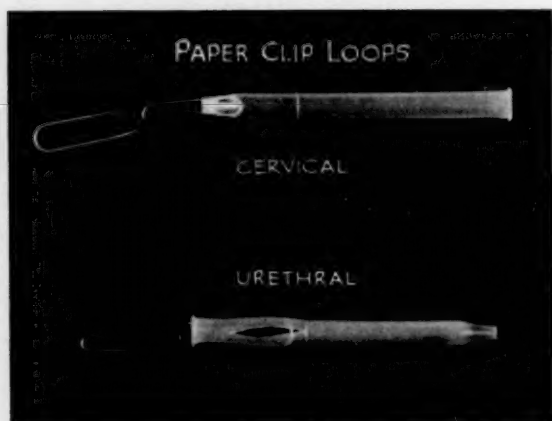


Fig. 1.

Some observers doubt that trichomonads may cause vaginitis, since they believe that the inflammatory reaction is actually produced by the bacteria which have replaced the normal lactobacilli.

Krönig in 1894 stated that antiseptic douches weaken or destroy the natural antiseptic action of the vagina. This was a profound, although little-noted, discovery. Tyler⁸ in 1959 stated that "an acid vaginal environment favors the maintenance of a healthy mucosa and helps to prevent infection from a variety of organisms."

I do not treat vaginitis without first making a diagnosis. In many cases this is impossible because the patient has recently douched. Usually, she is advised not to introduce anything into the vagina and to return in a week. It is surprising to see how many patients have improved by the time of the next examination and, in many cases, have been cured without therapy.

The most important part of treatment is to promote a normal vaginal physiology with its associated acid pH and lactobacillary flora. The only pathogenic microorganism which can exist under normal conditions is *Monilia*.

In this group of patients treatment consisted of daily insertion of vaginal suppositories of the 3 types of nitrofurans mentioned below. Length of treatment ranged between 1 and 4 weeks and was purposely terminated as soon as negative slides and/or cultures were ob-

tained. However, it is recommended that treatment should be carried through three menstrual periods with decreasing dosage between periods.

Three types of nitrofurans preparations were used in this study, thus automatically dividing the patients into three separate groups. Thirty-one patients were eliminated from the study because they did not return for follow-up examinations and one patient was eliminated because of a double infection of *T. vaginalis* and *H. vaginalis* in which only the former infection was cured. Five cases were transferred from the second to the third group.

The final results illustrated in Table II reveal a marked difference in the cure rate as the preparation was improved by adding nifuroxime,* an excellent fungicide which proved to be highly effective against *Candida (Monilia) albicans*. Further improvement in the cure rate was obtained when boric acid was added, probably because of its action in releasing both nitrofurans from a possible partial binding action of vaginal secretions and/or serum.

Comment

The importance of the psychological reactions of the patient should not be underestimated, and this phase of the treatment of vaginal disease has been stressed in the medical literature. However, the attitude of the physician has never been discussed, and I believe that this could be a very important factor in treatment. Many physicians regard the vagina as a repulsive organ; such an attitude is bound to affect the normal physician-patient relationship.

Histologic descriptions of the vagina present it as a normally functioning part of the body. The glycogen content of all tissues in the female genital tract need not be discussed; however, it is my contention that any solution introduced into the vagina produces a reduction in the glycogen content of its epithelium and, therefore, lowers it, thus producing a change in the basic

*Micofur, Eaton Laboratories.

Table II

	Cure	Failure	Reaction	Change treatment	Patient pregnant
Group I (nitrofurazone*)					
37 cases					
-1 (no follow-up)	22	7	4	0	2
-1 (Trichomonas-Hemophilus)	63% (App.)	20%	11%		6%
35					
Group II (furazolidone-nifuroxime†)					
44 cases	21	3	0	5	1
15 (no follow-up)	72%	10%		17%	3%
29					
Group III (furazolidone-nifuroxime-boric acid)					
96 cases	74	8			
14 (no follow-up)	90%	9%			
82					

*Furacin, Eaton Laboratories.

†Tricofuron Improved, Eaton Laboratories.

biochemical equilibrium and decreasing the defense mechanisms of the vagina against pathogenic invaders.

Conclusions

Treatment of vulvovaginitis must be topical, with the use of a cream or suppository with a water-soluble base, not only to help the vagina to destroy all pathogens, but also to restore its normal physiology.

Douches for any purpose must be eliminated completely. The patient must be instructed how to wash carefully the external genitals daily. It is advisable to use a soap containing a germicidal agent such as hexachlorophene.*

Nylon underwear must not be worn since it is nonabsorbent, and it should never be washed with detergents. The use of tampons should also be discouraged.

Emotional factors, particularly in patients with severe pruritus, must be considered and the use of tranquilizing drugs may be of value in treating the condition.

Self-administration of suppositories was the only treatment used except in Group I in which vaginal insufflations of nitrofurazone powder were given twice weekly as an

office procedure. It seems noteworthy that this was the only group that exhibited any reaction to the preparations.

Summary

Treatment of 146 patients with nongonococcal vaginitis with three different forms of nitrofurazone preparations prepared as vaginal suppositories was compared.

Causative organisms in this series were *T. vaginalis* (41 per cent), *C. albicans* (24 per cent), and *H. vaginalis* (35 per cent).

I wish to express my appreciation to the late Dr. Myles R. Miller and the Eaton Laboratories for their cooperation during this study.

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*pHisoHex, Winthrop Laboratories.

Vaginitis in childhood

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AN UNDERSTANDING of the physiology of the vagina in infancy and childhood is necessary in order to diagnose and treat pediatric vaginitis. At the time of birth the vagina of the child is quite thick, having 20 to 40 layers of stratified squamous epithelium, but differs from the adult vagina by the absence of cornification or maturity in the superficial cells. This great thickening of the squamous epithelium of the newborn is caused by estrogenic hormones produced by the placenta of the fetus. The vulva is enlarged at birth, and the skin of the body of the newborn (also affected by estrogenic hormone) is thick and resilient. At this time a white discharge composed of mucus and a profusion of hexagonal epithelial cells with small nuclei may be noted. The pH of the vagina of the newborn on the first day is 5.7, on the second day 5.6, the third day 4.9, and the fourth day 4.8.¹ Gradually the vagina becomes more alkaline; in 2 to 6 weeks after birth the pH of the vagina is 7.0, 7.5, or 8.0.

Cultures of the vagina of the newborn are sterile for the first 12 hours, then cocci appear which may not be cultured.² After 24 hours various cocci are found, and in 48

hours the Döderlein bacillus is present. Staphylococci, streptococci, and colon bacilli are found thereafter. The more acid pH occurring after 48 hours is produced by the fermentative effects of the Döderlein lactobacillus. However, the original acidity, though of lessened degree in the first 48 hours, could not be related to the lactobacillus since the organism is absent at that time; it is thought to be produced by the glycogenase in the serum, which ferments the glycogen to glucose, then the glycolytic enzyme in the squamous epithelial cells must change the glucose to lactic acid.¹

Fraenkel and Papanicolaou³ pointed out that after the first week of life the vaginal secretions contain increasing numbers of compact, round, or oval cells, as with the menopause, which indicate progressive atrophy of the epithelium. At 15 days there are atypical or transitional forms of squamous cells. The deep cells predominate in half of the cases, and in the remainder the smears are of the mixed type. Leukocytes are present constantly in varying numbers during this time, beginning a few days after birth. Round or oval cells alone are found when the infant is 4 to 6 weeks of age as a rule. The thick vagina caused by ovarian estrogens of the developing premenarchal young girl has large hexagonal epithelial cells with varying degrees of cornification, no pus cells, and fewer bacteria (less cocci in particular, but the reappearance of Döderlein's bacillus). The cultural findings in the newborn, prepubescent, pubescent, and adult woman vary with the amount of glycogen present. The

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variation in pH is related to the presence or absence of glycogen.

Etiology

Through the past half century and longer, the gonococcus has been incriminated as the chief etiological agent of vaginitis in childhood. At one time 80 per cent of cases of vaginitis in childhood were thought to represent gonorrhea, although some authors reported lesser numbers. The method of spread and recurrence of gonorrheal vulvovaginitis has never been satisfactorily explained.

Other specific organisms responsible for vulvovaginitis have been found on occasion. Diphtheria of the vagina, producing a typical membrane, occurs extremely uncommonly today. The pneumococcus has been cultured from vaginal discharge and rarely may be associated with pneumococcal peritonitis and pneumococcal pneumonia. Tuberculosis of the vulva and the vagina of the child was reported by Swain⁴ in 1934. Vincent's angina was described both by Brown and Barlow⁵ and by Pilot⁶ in single cases, but in each a foreign body was found (a lipstick holder and a hairpin). Lymphogranuloma venereum was reported by Levy.⁷ Primary herpetic vulvovaginitis occurred in cases reported by Slaven and Gavett⁸ and Krugman.⁹ Cytoplasmic inclusion bodies in the cells of the vagina¹⁰ were found in 9 of 42 children (only 2 had vaginitis), and in 41 of 174 women. These inclusion bodies were considered the same as those found in the nose and throat and associated in the latter areas with viruses which had been isolated. These investigators did not isolate the virus from the vagina. However, Mitchell and Dumpster¹¹ did find a Coxsackie virus in the vagina of one 7-year-old girl. *Shigella flexneri* was reported in one case by McGinness and Telling.¹² *Trichomonas vaginalis* has been found infrequently in the prepubescent child. Feo¹³ found the trichomonad in 3.6 per cent of Negro girls from 1 to 9 years of age.

Hardy² studied the bacterial flora of 16 premature infants, 81 unselected children in the wards of a children's hospital, and 93 children from a vaginal discharge clinic.

From these groups, 27 patients had Group A streptococcus; 22 had the gonococcus present and 14 had the diplobacillus of Pettit. The streptococcus and diplobacillus were thought related to concomitant infections of the respiratory tract. Ten patients had the same streptococcus in the nose as in the vagina, and in 8 of these the infections seemed related clinically. Hardy stated that among the patients studied, very few, apart from the premature group, should be considered normal. Pettit and Hitchcock¹⁴ reported on the normal flora of the prepubertal vagina in 46 children. They cultured diphtheroids in the majority of cases. *Streptococcus indifferens* was found in 28, *Str. viridans* in 18, *Str. faecalis* in 3, and *Str. hemolyticus* in 2. *Staphylococcus albus* was found in 24, *Staph. aureus* in 6, *Staph. epidermis* in 5, and *Staph. citreus* in 1. Micrococci were found in 10 cases, *Neisseria sicca* in 1, and finally, *Proteus* in 4 cases and *Escherichia coli* in 10 cases. These authors stated that only 2 patients of the 46 showed local inflammation in the vagina, and they pointed out that diphtheroids were more prominent than cocci.

Weaver¹⁵ described 15 children with vulvovaginitis attributed to *N. sicca*. By smears alone these organisms suggested gonococci; but by cultures and fermentation studies, he concluded that the disease in these children was not gonorrhea. This paper suggested that possibly the gonococcus was not the common cause of vulvovaginitis in children and that an error in identification had been made.

A larger proportion of cases at the present time are considered to have a nonspecific etiology, as no definite single agent has been incriminated as the causal agent.

Treatment

Twenty-five years ago and longer, the diagnosis of gonococcal vulvovaginitis was made frequently in gynecologic clinics and by pediatricians. A large percentage of cases of vulvovaginitis had the gram-negative intracellular, biscuit-shaped diplococcus. The remainder were considered of nonspecific origin. The treatment of gonococcal vulvo-

vaginitis 25 years ago was frustrating, because of the extremely long period of time required for cure. Treatment included douches with lactic acid solution, potassium permanganate, 1:10,000, and bichloride of mercury, 1:10,000.

Wrana,¹⁶ in 1935, suggested the use of a suction machine to remove secretions, after which the vagina was sprayed with a cleansing solution of green soap and lactura antiseptics. Boric acid solution, 2 per cent, frequently was used as an irrigation. Local applications two or three times weekly for months included silver nitrate in 3 to 5 per cent solution, Argyrol, Protargol, Dakin's solution, tincture of iodine, acriflavine, Mercurochrome (1 to 20 per cent solution), and silver picrate in suppositories and jellies. Crossen¹⁷ reported cures after diathermy. Others advised the use of vaccines of the gonococcus, with varying degrees of improvement. There was rarely hope of cure under 6 months of treatment, and the disease continued resistant, chronic, insidious, and recurrent.

Estrogenic therapy was introduced by Lewis,¹⁸ who reported on 8 patients treated with estrone (Theelin), 50 R.U. given at 1, 2, or 3 day intervals for 10 to 20 days. The gonococcus had disappeared at the end of 20 days in all 8 patients. Vaginal suppositories containing mixed equine estrogens were highly recommended by TeLinde and Brawner¹⁹ and subsequently by Lewis and Adler.²⁰ The latter reported 25 recurrences in 82 patients in a relatively short period of time, while Bensor and Steer²¹ had 50 per cent recurrences in 92 cases treated in this manner. Limper and Hieronymus²² recommended intramuscular estrogens, while Mazer and Shechter²³ had equally good results with intramuscular or vaginal estrogenic therapy. Side effects included growth of pubic hair, vaginal bleeding, and enlargement of the breasts, which occurred more frequently after the hypodermic injections. Pellet implantation of estradiol benzoate was performed in 18 patients by Holmes and associates,²⁴ of whom 5 developed breast enlargement, one increased growth of hair, and one bleeding.

In 1945 Compton and co-workers²⁵ reported complete cornification of the vaginal epithelium in 14 to 28 days of estrogenic therapy, but there were recurrences of gonorrhea in 25 per cent of 122 cases.

The sulfonamides were highly recommended for a period of time. Zahorsky²⁶ used sulfathiazole orally. Hac and co-authors²⁷ found that sulfapyridine, sulfathiazole, and sulfadiazine gave equally excellent results in 89 per cent of cases, whereas Mercurochrome instilled locally for 6 weeks had cured only 2 of 25 children. Schacht and Barber²⁸ advised sulfathiazole suppositories.

Penicillin was recommended for the treatment of vulvovaginitis in children by Sako, Tilbury, and Colley,²⁹ Clarke and Eisenberg,³⁰ McLean,³¹ and many others.

The importance of cervicitis was stressed by Andre.³² The cervix and vagina were examined routinely in 269 cases of vaginitis, of which 29 were gonococcal. With the Butterfield vaginoscope usually the cervix appeared edematous, hyperemic, with ectropion and erosion present. In the chronic state the cervix often was diffusely involved or there may have been only punctuate hemorrhages. Andre felt that cervicitis was one of the most common causes of recurrence. Fulguration of the cervix through the vaginoscope was advised in those cases. Rarely has there been any mention of the appearance of the cervix in cases of vaginitis; most authors have felt that the cervix was a barrier and was not involved in the gonococcal infection in the prepubescent child.

Rice and associates,³³ from the Department of Health of New York City, reported that 22 per cent of 715 children examined had vaginitis. Forty-one with smears showing gram-negative intracellular diplococci were given no treatment. Half recovered spontaneously by the seventh month. Of 33 patients treated with estrogenic substance, only one third were cured after 2 months of treatment. Of 53 patients treated with sulfanilamide, less than one half were cured after 9 days. Of 77 patients treated with sulfapyridine or sulfathiazole, seven eighths

were cured after 7 days. These authors concluded that there was no evidence of epidemics in the New York schools, that gonococcal vulvovaginitis is not as contagious as previously thought to be, that no instance of transmission of the disease by way of toilet seat had ever been proved, that the infection in the majority of cases was from an infected adult in the home (35 per cent of the girls between 6 years of age and puberty had admitted sexual contacts), that children should not be excluded from school because of gonococcal vulvovaginitis, that the disease does not require hospitalization, as previously practiced, that treatment with sulfathiazole may be recommended, and that the dictum that vaginitis spreads like wild-fire is not true. This extraordinary paper, and their second,³⁴ affected many of us to discount the importance of vulvovaginitis and to develop a laissez-faire attitude. As time has passed, we have concluded that minor inflammations of the vagina are so frequent as to be usual and not to require treatment, but that annoying irritations and discharges do require treatment.

Many continue to believe today that the modern and best treatment of vulvovaginitis, regardless of the origin, but particularly when caused by the gonococcus, is by the intramuscular administration of penicillin, but the frequent recurrence of inflammation, lack of improvement, and the recurrence of the gonococcus itself in a short period of time have led most practitioners to be distrustful of this therapy. While the sulfonamides undoubtedly proved of distinct value in the inhibition or eradication of many bacteria, including the gonococcus, in general, the success with this therapy has been even less than with penicillin. Discharge of nonspecific character, or recurrent with the gonococcus, has continued almost as a rule after these treatments. Cleanliness, avoidance of friction, observation of the small local irritation, and reassurance of the benignity of the condition have comprised the approach in the majority of cases, but those patients with obvious discharge and irritation require some form of therapy.

Report of cases

In the past 13 years 213 young patients have been studied and observed for vaginal inflammations. Eighty-one of these were private patients and had few cultural studies. One hundred and thirty-two were from our special vaginitis clinic in the University of Louisville Medical School and have had intensive microbiologic investigation. An earlier report on microbiologic studies was presented by Kotcher, Keller, and Gray³⁵ and a later clinical and microbiologic summary of the 200 cases were presented by Gray and Kotcher.³⁶ Of the present total cases 192 showed no effect of estrogenic hormone, as proved by the presence of round and oval epithelial cells in washings of the vagina taken with a medicine dropper. The pH of the vaginas varied from 7.0 to 8.0. Twenty-two of this group with atrophic prepubescent findings showed pale vaginas and very few pus cells. These were considered essentially normal and used as controls. The remaining 170 patients showed varying degrees of vaginitis.

Ten patients from 8 to 13 years of age complained of vaginal discharge and showed the full effect of estrogenic hormones. The vaginas were thick and the washings presented a profusion of large hexagonal epithelial cells with small nuclei. Evidently, the ovaries were secreting estrogen almost to a normal amount although menstruation had not begun. The findings in these cases were entirely similar to those in 11 additional patients who had been menstruating a few months and complained of vaginal discharge. In each of these there was also a full effect of estrogens. Thus, approximately 10 per cent of the young patients complaining of vaginal discharge had the hormone effect of estrogens. It is important that these types be differentiated before treatment is begun. In the group with already naturally occurring estrogens, the pH of the vagina varied from 4.0 to 6.5; this depended on the degree of vaginitis present.

The ages of the 213 patients varied from 3 months to 16 years. The majority were 6, 7, 8, and 9 years of age.

The symptoms of which the young patients complained included discharge in 153, irritation in 41, vaginal bleeding in 16, itching in 16, burning in the vagina in 10, frequency of urination in 7, nervousness in 7, and bed wetting in 5. Examination showed the vestibule to have a mild erythematous change, moderate redness, or a marked angry red granular appearance. The discharge varied from a slight white amount to a profuse yellowish white purulent secretion. In a few patients with severe discharge, the labia were edematous. The inflammation involved principally the mucous membrane of the vestibule and vagina.

Bacteriologic findings

Of these 213 patients, complete bacteriologic studies were made on 132 in the special vaginitis clinic. One hundred and fourteen from the latter showed a complete lack of estrogenic hormone, while 18 had thick vaginas indicating a strong estrogenic effect (9 were immediately premenarchal, and 9 had had their menarche recently).

Table I. Microbiologic findings from essentially normal vaginas of premenarchal girls with absence of any estrogenic hormone effect*

Organism isolated	No. of isolations	% of isolations
<i>E. vermicularis</i>	3	10.3
<i>N. perflava</i>	1	3.4
<i>Herellea</i>	1	3.4
<i>Str. viridans</i>	4	13.7
<i>Str. hemolyticus</i>	4	13.7
<i>Str. anhemolyticus</i>	7	24.1
Anaerobic streptococci	2	6.8
Enterococci	4	13.7
<i>Staph. aureus</i>	16	55.1
<i>Sarcina</i>	5	17.2
<i>E. coli</i>	5	17.2
Klebsiella-Aerobacter group	3	10.3
<i>Proteus</i>	2	6.8
<i>A. faecalis</i>	4	13.7
<i>Pseudomonas aeruginosa</i>	1	3.4
Döderlein's bacillus	1	3.4
Diphtheroids	16	55.1
<i>Bacillus subtilis</i>	1	3.4

*Number girls, 22; number observations, 29; age range, 6 months to 12 years; average age, 5.1 years; pH: 7.0 in 26 observations; 5.0 in 3 observations. Epithelium, round and oval cells; glycogen, none in cells as tested with iodine-containing solution (D'Antoni's).

Twenty-two girls with thin (atrophic) vaginas had essentially no vaginitis and they were considered as controls. Their ages varied from 6 months to 12 years. *Enterobius vermicularis* was found in 3, *Str. viridans* in 4, *Str. hemolyticus* in 4, *Str. anhemolyticus* in 4, enterococci in 4, *Staph. aureus* in 16, *E. coli* in 5, *Alcaligenes faecalis* in 4, Döderlein bacillus in one, and diphtheroids in 16 (Table I).

Gonorrhea was found in 18 patients of the group showing absent estrogenic effect (192 cases, which includes the private patients), an incidence of 9.3 per cent. Five with gonorrhea were private patients, and 13 were from the vaginitis clinic. This means 6 per cent of the private and 10 per cent of the clinic patients had gonorrhea. This organism was carefully distinguished from *N. sicca*, which was found only once in many cultures. This one positive culture occurred after this patient had been treated for some time. *T. vaginalis* was found in 5 (2.9 per cent) of the group with thin vaginas and in 4 (19.0 per cent) of the group with thick vaginas, a total of 4.2 per cent of the 213 cases.

A complete microbiologic study of 92 clinic patients with vaginitis, who showed no estrogenic hormone effect (Table II), revealed *E. vermicularis* in 25 per cent (only once from the vagina, the remainder from perianal impressions), diphtheroids in 72 per cent, Döderlein's bacillus in 8 per cent, *A. faecalis* in 13 per cent, *E. coli* in 27 per cent, Klebsiella-Aerobacter in 11 per cent, anaerobic streptococci in 10 per cent, enterococci in 12 per cent, *Str. anhemolyticus* in 23 per cent, *Str. hemolyticus* in 6 per cent, *Str. viridans* in 20 per cent, and *Staph. aureus* in 69 per cent. *Shigella flexneri* B was found in 2 per cent; *T. vaginalis* was found in 4.4 per cent, *Candida albicans* in 1 per cent, and yeast in 1 per cent. The remaining less common organisms are listed in Table II. No HeLa or monkey kidney cell agent or hemagglutinating virus could be found in any of those cases. Foreign bodies were present in 3 vaginas; 2 were safety pins and one a crayon.

It appears that the only specific organisms

Table II. Microbiologic findings in 92 cases with prepubescent atrophic vaginitis

Organism	92 patients	
	No.	%
<i>E. vermicularis</i>	23	25
<i>T. vaginalis</i>	4	4.4
<i>C. albicans</i>	1	1.1
Yeast	1	1.1
Gram-positive rods		
Diphtheroids	66	72.3
Döderlein's bacillus	8	8.7
<i>B. subtilis</i>	2	2.2
Gram-negative rods		
<i>A. faecalis</i>	12	13.1
<i>E. coli</i>	25	27.4
<i>E. Freundi</i>	2	2.2
<i>H. influenza</i>	1	1.1
<i>H. vaginalis</i>	0	0
Herellea	1	1.1
Klebsiella-Aerobacter	10	11.0
Flavobacterium	2	2.2
Paracolon	2	2.2
Proteus	3	3.3
<i>Ps. aeruginosa</i>	0	0
Mima	1	1.1
Gram-negative, unident	1	1.1
<i>Sh. flexneri B</i>	2	2.2
Gram-positive cocci		
Anaerobic streptococci	9	10.0
Enterococci	11	12.0
<i>Str. anhemolyticus</i>	21	23.0
<i>Str. hemolyticus</i>	6	6.5
<i>Str. viridans</i>	20	21.9
Sarcina	18	19.7
<i>Staph. aureus</i>	63	69.2
Micrococcus	1	1.1
Gram-negative cocci		
<i>N. gonorrhoeae</i>	13	14.2
<i>N. sicca</i>	0	0
HeLa cytopathogenic agent	0	0
Primary monkey kidney cell cytopathogenic agent	0	0
Hemagglutinating virus	0	0

are *N. gonorrhoeae*, *T. vaginalis* and possibly *Sh. flexneri B*. The remainder of the organisms appeared to have no infectious relationship, but to be secondary, probably arising from the intestinal tract and the nasopharynx. Many or all of these other organisms possibly are irritants and may cause inflammation in the thin vagina without estrogenic effect. But they are essentially all present in the vagina without active inflammation. Actually almost all vaginas from the young

with no estrogenic effect show some degree of inflammation.

The microbiology of the 18 patients with thick vaginas and a strong estrogenic effect in which cultures were done (9 normal and 9 abnormal) is quite different (Table III). Diphtheroids were found in 3, yeast in 3, *C. albicans* in 3, *T. vaginalis* in 4, Döderlein bacillus in 15, *E. coli* in 3, *A. faecalis* in 1, and *E. vermicularis* in 3. The details of the microbiology of these two groups are to be noted in Table III. While all 18 patients in the group with estrogenic effect who had cultural studies complained of discharge, 9 were normal, having a mucous secretion containing only large hexagonal cells with no pus cells. Eight had vaginitis, 4 caused by *Trichomonas*, 2 by *Candida*, and 2 unknown. It is of interest that 9 of the patients were premenarchal, varying in age from 8 to 14 years, but had the thick vagina. The remainder had recently begun to menstruate.

Treatment

Treatment in these cases included penicillin in 12, streptomycin in 2, and sulfonamides in 4. In each instance the patients appeared temporarily improved but soon had a recurrence of the discharge. When the gonococcus was present, this organism seemed to recur rapidly.

Estrogenic hormone in various forms was used as treatment in 145 patients with thin vaginas without estrogenic effects. This includes those from the private group. The estrogen was prescribed orally in 23 patients as conjugated equine estrogens,* 0.3 mg. daily, and in 4 instances as diethylstilbestrol, 0.1 mg. daily. Twenty-four of these patients developed thick vaginas with desquamation of large hexagonal epithelial cells and a complete disappearance of pus cells and symptoms. Suppositories containing mixed equine estrogens† were given to 17 patients, and 14 developed a full effect of estrogens under our observation. In 7 of these there

*Premarin, Ayerst Laboratories, New York, New York.

†Amniotin, E. R. Squibb & Sons, New York, New York.
Estrogenic suppositories, The Upjohn Company, Kalamazoo, Michigan.

Table III. Microbiology of vaginas from 18 patients showing effect of their own estrogenic hormones

Organism	No vaginitis (9)				Vaginitis (9)			
	Premenarchal (6)		Menarchal (3)		Premenarchal (3)		Menarchal (6)	
	No.	%	No.	%	No.	%	No.	%
<i>E. vermicularis</i>	1	16.6	0	0	0	0	2	33.3
<i>T. vaginalis</i>	0	0	0	0	0	0	4	66.6
<i>C. albicans</i>	0	0	0	0	1	33.3	1	16.6
Yeast	0	0	0	0	1	33.3	2	33.3
Gram-positive rods								
Diphtheroids	1	16.6	0	0	1	33.3	1	16.6
Döderlein	4	66.6	3	100	3	100	5	83.4
<i>B. subtilis</i>	0	0	0	0	0	0	0	0
Gram-negative rods								
<i>A. faecalis</i>	0	0	0	0	1	33.3	0	0
<i>E. coli</i>	2	33.8	0	0	0	0	1	16.6
<i>E. freundii</i>	0	0	0	0	0	0	0	0
<i>H. influenzae</i>	0	0	0	0	0	0	0	0
<i>H. vaginalis</i>	0	0	0	0	0	0	0	0
Herellea	0	0	0	0	0	0	0	0
Klebsiella-aerobacter	0	0	0	0	0	0	0	0
Flavobacterium	0	0	0	0	0	0	0	0
Paracolon	0	0	0	0	0	0	0	0
Proteus	0	0	0	0	0	0	0	0
<i>Ps. aeruginosa</i>	0	0	0	0	0	0	0	0
Mima	0	0	0	0	0	0	0	0
<i>Sh. flexneri B</i>	0	0	0	0	0	0	0	0
Unidentified	0	0	0	0	0	0	0	0
Gram-positive cocci								
Anaerobic streptococci	0	0	0	0	0	0	0	0
Enterococci	1	16.6	0	0	0	0	1	16.6
<i>Str. anhemolyticus</i>	1	16.6	0	0	0	0	0	0
<i>Str. hemolyticus</i>	1	16.6	0	0	1	33.3	1	16.6
<i>Str. viridans</i>	0	0	0	0	0	0	0	0
Sarcina	1	16.6	2	66.6	1	33.3	0	0
<i>Staph. aureus</i>	3	50.0	2	66.6	3	100	1	16.6
Micrococcus	0	0	0	0	0	0	5	83.4
Gram-negative cocci								
<i>N. gonorrhoeae</i>	0	0	0	0	0	0	0	0
<i>N. sicca</i>	0	0	0	0	0	0	0	0
HeLa cells cytopathogenic	0	0	0	0	0	0	0	0
Primary monkey kidney cell cytopathogenic agent	0	0	0	0	0	0	0	0
Hemagglutinating virus	0	0	0	0	0	0	0	0

was recurrence of the vaginitis in the few months follow-up.

The estrogenic cream, containing conjugated equine estrogens, was used in 101 cases. The mothers were each instructed to apply the cream to the vulva and vestibule of the child each night for 2 weeks, then on alternate nights for 2 weeks, then twice weekly for 2 months. As a rule this produced

and maintained the thick acidified vagina. After 2 to 4 weeks a white discharge composed of mucus containing large hexagonal epithelial cells without pus cells appeared. When the secretion was excessive, the hormone application was reduced. Too frequent applications caused edema of the vulva and slight enlargement of the breasts. This was avoided by observation of the patient.

Vaginal bleeding did not appear in any patient treated with estrogenic cream.

Forty-five of those treated with estrogenic cream were observed by us to develop a complete change in the vagina with disappearance of pus cells after 2 to 6 weeks of therapy. Twenty-five patients, making a total of 70, were followed by their pediatricians to a satisfactory cure. Nineteen patients had an improvement of the vagina but not the strong and complete effect of estrogens, and this was thought related to inconstant use of the hormone cream. Thirteen patients from the clinic group either were not followed or showed no effect from the treatment. In most of these it appeared obvious that the mother was not applying the medication. The gonococcus was eradicated in each of the 18 cases who received only estrogenic therapy. Recurrence or reinfection was found in 3 cases.

Of the total number of patients with thin vaginas without estrogenic effect, there were 35 who maintained a full effect of estrogens from the local estrogenic cream for at least 4 weeks. The cultural findings are shown in Table IV. This table compares the cultures before treatment with those after a maintained estrogenic state. It is of interest that the pinworm diminished slightly in number, but this has a variable incidence. The incidence of *T. vaginalis* was not changed, and the clinical course of vaginitis produced by this organism was not affected by the hormone therapy. *C. albicans* and yeast were slightly more frequent in the estrogenic habitat. Diphtheroids decreased from 65 to 37 per cent, but this organism ordinarily has not been considered pathogenic. Döderlein bacillus increased from 11 to 68 per cent, which is a normal change. *E. coli* decreased from 28 to 5.7 per cent, and this may well mean the removal of an irritant, although serotyping by antisera of four enteropathogenic stains, 026:B6, 055:B5, 0111:B4, and 0127:B8, showed only one normal child to have agglutination in antiserum of 026:B6. This does not mean the nonenteropathogenic *E. coli* were impossible of causing inflammation in the vagina. *Sh. flexneri B* was

Table IV. Microbiology of 35 patients with prepubescent atrophic vaginitis (before and after 4 weeks' treatment with conjugated equine estrogenic cream)

	Before		Estrogenic at height of estrogenic effect	
	No.	%	No.	%
<i>E. vermicularis</i>	9	25.7	6	17.3
<i>T. vaginalis</i>	3	8.5	3	8.5
<i>C. albicans</i>	0	0	1	2.8
Yeast	1	2.8	2	5.7
Gram-positive rods				
Diphtheroids	23	65.7	13	37.1
Döderlein	4	11.4	24	68.5
<i>B. subtilis</i>	0	0	1	2.8
Gram-negative rods				
<i>A. faecalis</i>	1	2.8	1	2.8
<i>E. coli</i>	10	28.5	2	5.7
<i>E. freundii</i>	0	0	0	0
<i>H. influenzae</i>	0	0	0	0
<i>H. vaginalis</i>	0	0	0	0
Herellea	0	0	0	0
Klebsiella-Aerobacter	3	8.5	2	5.7
Flavobacterium	2	5.7	1	2.8
Paracolon	0	0	1	2.8
Proteus	0	0	1	2.8
<i>Ps. aeruginosa</i>	0	0	0	0
Mima	0	0	1	2.8
<i>Sh. flexneri B</i>	2	5.7	1	2.8
Unidentified	0	0	2	5.7
Gram-positive cocci				
Anaerobic streptococci	0	0	1	2.8
Enterococci	2	5.7	1	2.8
<i>Str. anhemolyticus</i>	9	25.7	5	14.2
<i>Str. hemolyticus</i>	1	2.8	2	5.8
<i>Str. viridans</i>	6	17.3	5	14.2
Sarcina	4	11.4	6	17.3
<i>Staph. aureus</i>	17	48.5	25	71.4
Micrococcus	1	2.8	2	5.8
Gram-negative cocci				
<i>N. gonorrhoeae</i>	3	8.5	0	0
<i>N. sicca</i>	0	0	0	0
HeLa cell cytopathogen	0	0	0	0
Primary monkey kidney cell cytopathogenic agent	0	0	0	0
Hemagglutinating virus	0	0	0	0

maintained in one of 2 cases here, but it subsequently disappeared by further local estrogenic therapy.

Str. anhemolyticus decreased from 25 to 14 per cent, while *Str. hemolyticus* and *Str. viridans* remained nearly the same. *Staph.*

aureus increased from 48 to 71 per cent in these patients supposedly cured of all vaginitis by estrogenic therapy alone. The explanation of this is not available. Here this organism would seem not to be an irritant, at least not when the vagina is so thick and acid. The gonococcus disappeared in the 3 involved in these 35 cases. No cytopathogenic agent for HeLa or monkey kidney cells or hemagglutinating virus could be found in any case before or after treatment.

This local estrogenic therapy in the form of a cream applied to the vulva and vestibule was followed by clinical cure and by disappearance or decrease in most of the organisms except *T. vaginalis* and *Staph. aureus*. Perhaps diphtheroids, *E. coli*, and also *Str. anhemolyticus* are irritants in the thin and alkaline vagina.

Of the 10 premenarchal patients with thick vaginas, indicating the effect of estrogenic hormones, who complained of vaginal discharge, 6 showed normal epithelial cells of the large hexagonal type and no pus cells (Table III). These patients did not have vaginitis or cervicitis, but were brought to the physician because of a white discharge which proved to represent a normal physiologic secretion produced by their own ovaries. Four of these patients had true vaginitis; in 2 this was due to *C. albicans*; in one yeast was cultured, and one patient would not cooperate. These were the same situations which occur in adult women. Three were treated satisfactorily by phenylmercuric acetate. The fourth patient would not cooperate for complete study.

Of the 11 patients who had been menstruating for a few months, who complained of discharge, 4 were normal; the secretions showed large hexagonal cells with no pus cells. Again this was a physiologic secretion and required no treatment. Microscopic examination was necessary to determine this point (and this applied to the adult in quite the same circumstance). Seven patients showed true vaginitis. In 4 this was caused by *T. vaginalis*, in one by *C. albicans*, and in 2 by yeast. Three of the patients with trichomoniasis were cured by acetarsone, but one

had recurrence and one patient refused treatment. The patients with *Candida* and yeast infections were cured with phenylmercuric acetate. The ages of these children varied between 11 and 13 years.

Summary and conclusions

1. An understanding of the physiology of the vagina is necessary in the clinical approach to vaginal inflammation in children. The vagina is thick, sheds glycogen, and produces acid at birth, but in 2 to 6 weeks it becomes thin and alkaline. Numerous bacteria invade the vagina after this state is reached. Vaginitis in degree in the prepubescent child with atrophic vagina occurs exceedingly frequently. In the few months or year or two before the menarche, the vagina becomes thick and again produces glycogen and becomes acid. Discharge then may represent normal mucus or may result from an adult type of infection.

2. Of 213 cases in this series, 81 were in private patients and few cultures were taken. On the other hand, 132 clinic patients had complete microbiological studies (Tables I, II, III, IV). In 22 young patients with essentially normal, thin, atrophic vaginas, the variety of organisms were similar to those found in 92 cases, also showing no effect of estrogenic hormone, but with definite vaginitis.

3. In the 92 prepubescent patients with thin vaginas and vaginitis, microbiologic study revealed the gonococcus in 9.3 per cent, *T. vaginalis* in 2.9 per cent, *Sh. flexneri B* in 1.4 per cent, and bacteria of various species found in the intestinal tract and nasopharynx in the majority. Foreign bodies were found in 1.6 per cent.

4. Thirty-five patients with thin vaginas and atrophic smears, treated with estrogenic cream applied to the vulva, had greatly diminished numbers of organisms after the estrogenic state had been maintained for 4 weeks.

5. Twenty-one patients of the total had vaginas that were thick, with effect from their own estrogenic hormone (10 were premenarchal and 11 had recently menstruated

for the first time). The variety of organisms in the 18 cultured was much decreased, as compared with those having no estrogen.

6. Estrogenic hormone was used as treatment on 145 patients with prepubescent atrophic vaginitis. Estrogenic cream applied locally to the vulva and vestibule in 101 patients produced cure in 70 and improvement in 19, while 13 showed no change or were not followed sufficiently. It was concluded that the cream was quite effective if applied

as directed. Recurrence of vaginitis in degree commonly occurred, and retreatment with estrogenic cream frequently was necessary.

7. Prepubescent atrophic vaginitis disappears with the menarche or after the child's own estrogenic hormone appears before the menarche to produce the thick vagina, glycogen, and acidity. After that time, vaginitis, when present, simulates that found in the adult, and usually is caused by *T. vaginalis* or *C. albicans*.

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Vaginal candidiasis

Study of comparative therapeutic results in obstetrical
and gynecological patients

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NUMEROUS studies have presented statistical evidence that moniliasis occurs more often in obstetrical patients,^{1,7} but reports concerning results in pregnant versus non-pregnant women appear to be infrequent. The impression has been that it is far more difficult to obtain a clinical and culture-proved cure in the pregnant woman than in other patients. Apparently, the glycogen-rich and vascular vaginal epithelium during pregnancy is particularly well suited to persistent inhabitation by *Candida albicans*, which is the most common cause of vulvo-vaginal mycoses. The gynecology patient with candidiasis may experience increased symptoms during the premenstrual phase when vaginal cells contain high glycogen levels. This microorganism often exhibits pathogenicity in patients with uncontrolled diabetes, thus lending additional evidence to the belief that increased glycogen in tissues may be a predisposing factor in this infection. The purpose of this study was to evaluate the effectiveness of a new vaginal cream, chlordanol,* in the treatment of candidiasis concurrently, in equal numbers of obstetrical and gynecological patients. It was felt that a

comparison of results obtained with identical therapy in both types of patients would indicate whether pregnant women with candidiasis actually are more difficult to cure.

The vaginal cream evaluated in this series contained 1 per cent chlordanol as its active ingredient. This recently synthesized organic compound is said to be a potent fungicide rather than a fungistatic agent.³ The effectiveness of chlordanol against *C. albicans* is reported to be due to 3-trichloromethylthio-5-(1-ethyl) amylhydantoin. The latter radical seems to be responsible for the successful penetration of the fungus cell membrane. Recently published studies, in which this drug was used to treat vaginal candidiasis, showed good to excellent results.^{2,4} However, Nathanson⁶ found that a fairly high percentage of patients required more than one course of chlordanol therapy before negative cultures could be obtained.

Materials and methods

All patients included in this study were from our private practice. Each complained of pruritis and, upon vaginal examination, most of the patients had a vaginal discharge which varied in appearance from cheeselike to a milky white. Irritation and edema of the vulva were commonly seen. In some patients, the vaginal mucosa was fiery red.

A specimen for culture was taken to establish the presence of *C. albicans* in each

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*Sporostacin, Ortho Pharmaceutical Corporation, Raritan, New Jersey.

patient. To obtain this, a nonlubricated speculum was inserted in the vagina and sterile cotton-tipped applicators were used to secure particles of the discharge. If, in the course of this study, there was no discharge present, the applicators were swabbed about in the posterior and lateral vaginal fornices.

The material thus obtained was transferred immediately to the surface of a tube of Nickerson's medium.* The use of this culture medium has been shown to provide a simple, specific method of diagnosing candidiasis in an office practice.⁵ Bacteria usually do not grow on Nickerson's medium, nor does the inoculated medium require incubation beyond room temperature. In positive cultures, *C. albicans* usually appears in 1 to 3 days as dark brown to black colonies. The cultures were not considered as negative until 5 days had passed without growth of the distinctive appearing colonies.

Each of the patients included in the study had a positive culture of *C. albicans*. After the organism was found and initial therapy started, the patients were given instructions for the intravaginal use of 5 c.c. (one applicatorful) of chlordanoin cream twice daily for 14 days. Each patient was asked to return one week following completion of therapy for repeated study of cultures for *Candida*.

Results

The data in Table I present the over-all cure rate as shown by negative vaginal cultures. Although this study began with 56 obstetrical and 53 gynecological patients, the "drop out" rate was fairly high among the nonpregnant patients who developed clinical relief but did not return for the final culture studies. Thus, the corrected totals are shown as 55 obstetrical and 38 gynecological patients.

In the obstetrical group, clinical cures and negative cultures were obtained in 33 cases (60 per cent), while 22 patients (40 per cent) showed the presence of culturable

Candida. In the gynecological series, 30 women (79 per cent) showed negative cultures and only 8 (21 per cent) revealed positive growths of *Candida* colonies.

When the clinical results are tabulated, regardless of the findings in the cultures, it can be seen in Table II that the patients demonstrated a high rate of clinical improvement. However, these results were not permanent unless they were accompanied by negative cultures for *Candida*. In 3 gynecological cases, the patients were not observed nor were they contacted to determine the results of the therapy. These are classified among the "unknown results." In an additional 12 cases, contact was made by telephone concerning the clinical results. These, however, did not return for their final culture studies. In the obstetrical series, only one patient failed to return for the final culture, but she was contacted by telephone concerning her clinical condition. Thus, the total number of patients in Table II is 106. When the 80 per cent "clinical cures" of the obstetrical series is compared to the 86 per cent of the gynecological series, it can be seen that approximately the same good clinical results were obtained in both groups of patients after three courses of therapy. The tendency, however, was to find a more rapid clinical result in somewhat greater frequency among the nonpregnant patients.

More than one course of therapy was found necessary in some of the affected women. Table III shows the results obtained in the 93 patients of this study. There is a marked difference in the responses of both series to the therapy on the first 14 day course of treatment. The "cures," as demonstrated by both clinical results and negative cultures, were greater among the gynecological patients (60.5 per cent) than the obstetrical cases (23.6 per cent). It was only after the third course of therapy that the obstetrical patients showed an equivalent 60 per cent negative culture findings. The incidence of refractory cases, even after 3 courses of treatment, was almost twice as great among the obstetrical series.

*Ortho Pharmaceutical Corporation, Raritan, New Jersey.

Table I. Incidence of negative cultures

<i>Total cases</i>	<i>Unknown results</i>	<i>Corrected total</i>	<i>Negative culture</i>	<i>Positive culture</i>
<i>Obstetrical patients</i>				
56	1	55	33 (60%)	22 (40%)
<i>Gynecological patients</i>				
53	15	38	30 (79%)	8 (21%)

Table II. Clinical results following treatment

<i>Total cases</i>	<i>Unknown results</i>	<i>Corrected total</i>	<i>Clinical cure</i>	<i>No clinical cure</i>
<i>Obstetrical patients</i>				
56	0	56	45 (80%)	11 (20%)
<i>Gynecological patients</i>				
53	3	50	43 (86%)	7 (14%)

Table III. Incidence of negative cultures among treated patients

Total cases	No. of therapy courses needed to show negative cultures			Refractive after 3 courses
	1	2	3	
Obstetrical patients				
55	13	5	15	22
Gynecological patients				
38	23	5	2	8
Total	36	10	17	30

Comment

The use of chlordanoin cream for the treatment of vulvovaginal candidiasis resulted in rapid clinical relief in the majority of patients in this series. However, the desirable clinical results were not always accompanied by negative vaginal cultures for *Candida*. Those patients who failed to show negative cultures tended to relapse into the clinical disease when therapy was discontinued before vaginal cultures became negative for *Candida*. In 12 gynecological patients, a rapid relief from dyspareunia, burning, and itching was observed before these patients voluntarily discontinued their office visits and, consequently, were not studied for final cultures for *Candida*.

It was not difficult to obtain the cooperation of the patient and to teach her the proper use of the cream, as chlordanoin is a white cream that is odorless, nonstaining, and

esthetically acceptable. The rapid relief from intense symptoms resulted in excellent co-operation during this study.

The incidence of allergic manifestations which could be attributed to the therapy was judged to be extremely low. It should be emphasized that in the presence of secondary infection and severe excoriation of the vulva, it is difficult to diagnose true allergic reactions. In one instance, a patient complained of increased itching following treatment and, consequently, the therapy was discontinued.

Even though the repeated use of chlordanoin did not produce a negative culture in all of the cases, it was found to give a high percentage of cures, as demonstrated by negative cultures, with an even higher percentage of clinical relief. The reasons for the refractoriness of some cases to the treatment were not studied. These, of course,

would include the possibility of reinfection by the marital partner or by the patient's environment.

The results tend to confirm the observations made in the past that obstetrical patients with candidiasis are harder to cure than others. In this series, a single course of treatment resulted in over 60 per cent cures in the nonpregnant group, as shown by cultures, and this percentage was increased to 79 per cent by the completion of the third course, leaving only 8 cases (21 per cent) refractory to 3 courses of clordantoin therapy. The obstetrical series, however, achieved only 23 per cent cures after the first course of therapy, but it was raised to 60 per cent by the third course of treatment. In addition, it seemed that response was quicker and more satisfactory among the nonpregnant women. The pregnant women with candidiasis developed rapid

clinical relief, but they were much slower to show negative vaginal cultures.

Summary

Comparative results in the treatment of vaginal candidiasis in obstetrical and gynecological patients are presented. As has been observed by others, the pregnant patient is more difficult to cure than the nonpregnant one. In the latter group, a single 14 day course of treatment resulted in 60 per cent cures, as demonstrated by negative cultures for *Candida*, while the obstetrical cases showed only 23 per cent. At the end of the third course of therapy, both groups showed a good result, with a 60 per cent cure rate in the pregnancy cases and 78 per cent in the gynecological cases. The incidence of clinical relief and improvement among the 93 patients was even higher than the number of cures, as was evidenced by cultures.

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Modification of the vaginal hysterectomy technique for the treatment of uterine prolapse

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THE correction of the defects which develop in the female pelvic supporting structures prove to be a continuing challenge to the gynecologic surgeon. The endopelvic fascias upon which the female pelvic organs depend for much of their support are intrinsically weak. Teleologically they seem to be designed hopefully to give support, yet to be sufficiently yielding to give way gracefully under the forces of labor. This apparent compromise in function not only results in defects that may occur after easy uncomplicated labors but also accounts for an uncomfortable number of our failed repairs in spite of the most meticulous techniques and detailed attention to pre- and postoperative care. It is well known to the gynecologist of experience that these repairs all too frequently appear quite differently at the first follow-up visit than they do after several years have elapsed when the stresses of an active existence have fully tested the adequacy of the reconstructive operation. Of the various conditions that we treat by some sort of vaginoplastic procedure, the incidence of failures seems greatest in the symptomatic relief of urinary stress incontinence and in the anatomic cure of the more extensive degrees of uterine prolapse. This communication deals with the latter condition.

There are two operations that are currently favored in the United States for the

cure of prolapse, the so-called Manchester operation and the vaginal hysterectomy with vaginoplastic reconstruction. In our clinic both operations have been used and our results show a greater number of failures attributable to the vaginal hysterectomy. However, this comparison is not at all valid because, with the exception of the poor-risk old women who are treated by some vaginal occlusive procedure, patients with the more extensive degrees of prolapse are now practically always managed by the vaginal hysterectomy operation while those with the lesser degrees of prolapse are more generally treated by some modification of the Manchester procedure. For this reason, the smaller number of failures chargeable to the Manchester operation does not convince us that we should more generally adopt it. Actually, it is difficult for us to understand how the Manchester operation can cure the major degrees of prolapse. This operation seems to achieve so little in the actual reconstruction of the pelvic supports that one is inclined to believe that the good results obtained are largely dependent on the amputation of an elongated cervix, the development of a variable degree of scar tissue around the remaining cervix, and the support that is further developed by a substantial closure of the vaginal hiatus in the levator diaphragm. With this kind of thinking, we have endeavored to improve our results in the more extensive degrees of uterine prolapse by revising our vaginal hysterectomy technique rather than by the more general use of the Manchester procedure.

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The vaginal hysterectomy at least makes it possible to have complete access to all the attenuated uterine supports and to bring these together to form a central point of attachment for the vagina that is as strong as the inherent strength of the ligaments will permit. In addition, the vaginal hysterectomy allows for the repair of the variable degrees of enterocele which are usually present in these advanced cases.

In a study of 61 patients on our ward service, followed from 1 to 3 years, in whom a vaginal hysterectomy had been done for uterine prolapse, the incidence of poor results consisting of either a significant degree of cystocele, enterocele, or vaginal prolapse was about 11.5 per cent. This group of cases represents the more advanced types of prolapse with evidence of the cervix and at least part of the uterus protruding beyond the introitus. They made up a little less than one half of the ward service vaginal hysterectomies with vaginoplasty done over a 5 year period. These failures were not all evidenced by a vaginal protrusion but it is conceivable that with more time the patients would consider the operation unsuccessful. An additional point should be made about these results. It is quite apparent from a review of these records that there were more failures in the women who were left with a functional vagina than in the older women in whom by a technique of overcorrection, especially in dealing with the posterior repair, the vagina had been considerably shortened and narrowed. If these overcorrected cases were omitted from the total group and the incidence of satisfactory results were based on a full 3 year follow-up of women operated upon for a complete prolapse and left with an adequately functional vagina, I would estimate that not more than 80 per cent would be considered to have a satisfactory result. This is more like the figure by which the gynecologic surgeon will measure his results. This is the figure that currently challenges his best efforts to cure these women.

The techniques employed in performing our cases were largely the modifications of

the Mayo¹ technique. These modifications consist essentially of adding two steps to the original operation: (1) greater attention is directed to uniting the uterosacral ligaments to one another and closing the pouch of Douglas; (2) the united broad ligaments are brought well up under the bladder and joined to the pubocervical fascia to give the cystocele repair more support. These modifications have been described very well by a number of able gynecologists including Ward,² Danforth,³ and Emmert.⁴

With a background of chronic dissatisfaction with our results built up in the course of a long experience in the consultation clinic where the failures are sent for disposition, there was always the desire to improve our techniques whenever one of these operations was performed. In the performance of a vaginal hysterectomy about 2 years ago in an elderly patient according to this modified Mayo technique, the ligaments available for the reconstructive part of the procedure after the uterus had been removed were so attenuated that the operation seemed destined to failure unless a vaginal occlusive procedure was carried out. When the removed specimen was examined later, the thought occurred that perhaps the most substantial parts of the cardinal and uterosacral ligaments, the actual insertion of these ligaments in the cervix, had been removed. A number of cases were subsequently studied in which sections were taken through the cardinal ligaments and cervix. These were obtained from specimens removed by radical hysterectomy. Differential staining showed that these ligaments contained very little fibrous tissue until the cervix was reached, at which point they more nearly approached the proportion of fibrous tissue characteristic of the cervix itself as described by Danforth.⁵ It was on the basis of these thoughts and observations that the modification of the vaginal hysterectomy here described was developed.

Technique

1. Eight cubic centimeters of a 1:20,000 phenylephrine (Neo-Synephrine) solution is

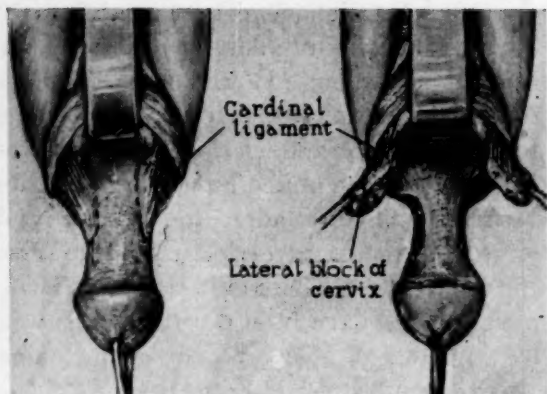


Fig. 1. Step 6. Manner of developing lateral cervical blocks with cardinal and uterosacral ligaments remaining attached. Bleeding is controlled with figure-of-eight sutures placed in the substance of the cervix.

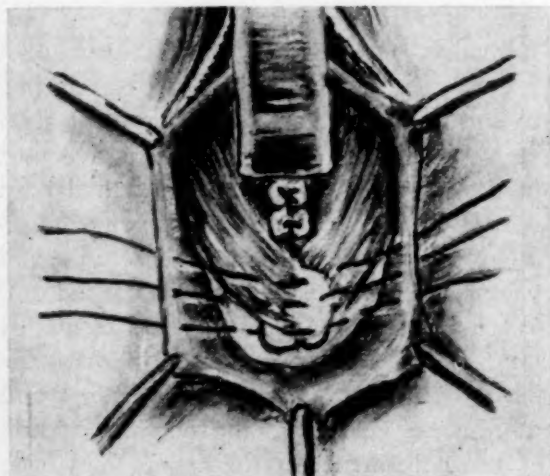


Fig. 2. Step 15. Manner of placing holding sutures through the vagina, the crossed and joined cervical blocks, and the posterior peritoneum. These sutures should be of No. 1 chromic catgut because should they break it would be difficult to replace them after the pubocervical fascia has been closed.

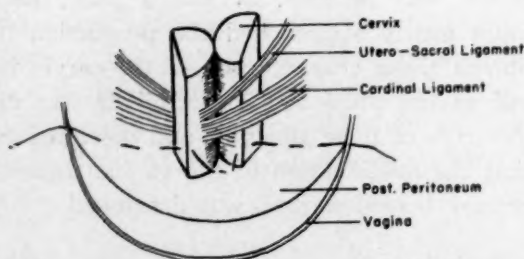


Fig. 3. Step 15. Diagrammatic representation of crossed cervical blocks and method of placing one of the holding sutures shown in Fig. 2.

injected into each paracervical space. This seems to decrease blood loss in the first few steps of the operation.

2. A circular incision is made completely around the cervix and through the entire thickness of the vaginal mucosa at a point just below the lowest limit of the bladder as determined with the bladder sound.

3. The vaginal mucosa with bladder is pushed up all around while traction is made on the cervix. This is done by blunt dissection with the thumb covered by gauze sponge and continued until the anterior peritoneal fold and the peritoneum of the pouch of Douglas come into view.

4 and 5. Both folds of peritoneum are entered, cut transversely, and tagged with a suture.

6. At this point, instead of clamping, ligating, and cutting the bladder pillars and the cardinal and uterosacral ligaments, these structures are separated in mass from the uterus by cutting into the cervix in such a manner that lateral blocks of cervical tissue are developed. These blocks should be about 2.5 cm. long and should be made up of the most superior portion of the cervix just below the entrance of the uterine vessels into the uterus. The width of the blocks will depend upon the width of the cervix but, in any event, they should not include any part of the mucosa of the cervical canal. Bleeding which occurs from the cut surfaces of the cervical blocks is controlled with figure-of-eight sutures through the blocks rather than by sutures around the ligaments (Fig. 1).

7. The uterine vessels are ligated, cut, and religated.

8. The fundus is delivered and the upper broad ligament with its contained round ligament, tube, and uteroovarian ligament is clamped and cut on each side to remove the uterus.

9. The ovaries are inspected.

10. Each upper broad ligament pedicle is separately suture ligated, then approximated one to the other with several interrupted sutures. The hemostatic sutures are cut while the approximating sutures are held.

11. The anterior peritoneal fold is attached to the upper broad ligament with a half purse string in such a manner that the stumps are extraperitonized.

12. The anterior vaginal wall is opened in the midline to the base of the urethral orifice, flaps are turned laterally, and the pubocervical fascia covering the bladder developed to its origin at the pubic rami.

13. The cervical blocks are crossed over each other and sutured together in this crossed position. These sutures are held.

14. Excess vagina of the anterior wall is cut away.

15. Two or three sutures are then placed which will incorporate vagina, the joined cervical blocks, and the posterior peritoneum. The peritoneal sutures are placed in the nature of a half purse string with two or three bites being taken before and after entering the crossed cervical blocks. This step is carried out at this time before closure of the pubocervical fascia so that the pouch of Douglas can be better visualized. These sutures are not tied at this time (Figs. 2 and 3).

16. The pubocervical fascia is united over the bladder with special care to elevate the vesical neck with mattress sutures (Kelly stitches).

17. Before the last sutures are placed in the pubocervical fascia the united broad ligaments are transposed into the anterior wall repair as high up as they can be conveniently sutured without tension to the underlying pubocervical fascia (Fig. 4).

18. The closure of the pubocervical fascia is completed with the last few sutures brought into the upper part of the cervical blocks.

19. Sutures that were placed in Step 15 are tied.

20. The remainder of the vagina is closed.

21. The posterior wall is repaired with or without placing the upper levator muscle suture into the cervical blocks depending upon the need for a functional vagina (Fig. 5).

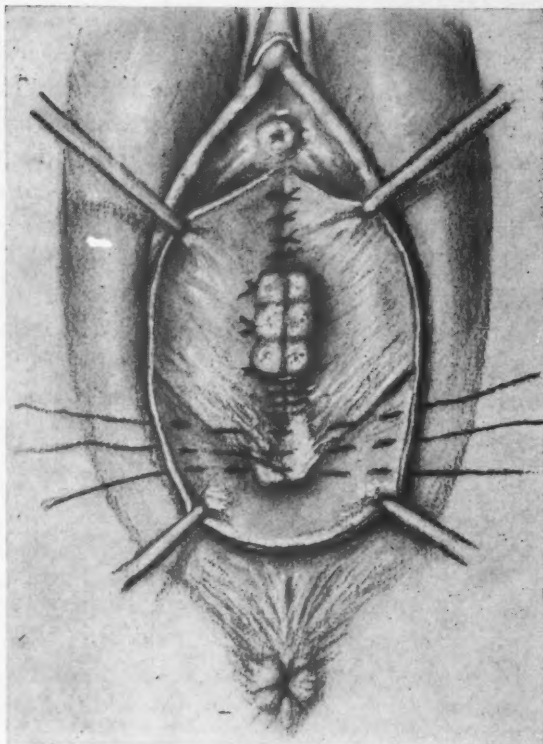


Fig. 4. Step 17. Transposition of upper broad ligaments to the front of bladder and pubocervical fascia.

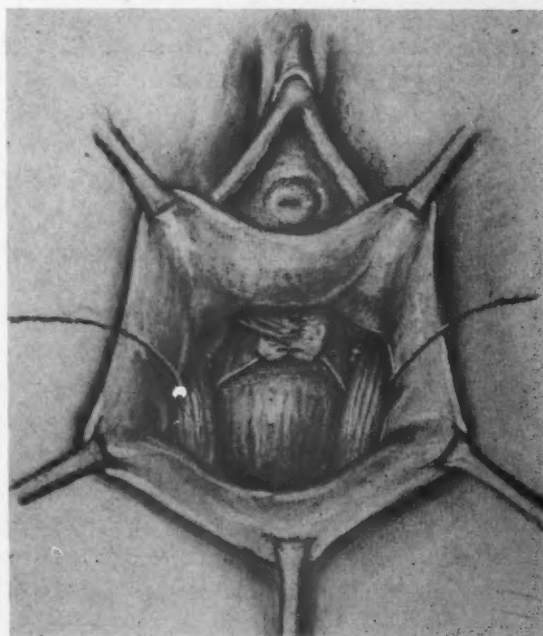


Fig. 5. Step 21. The posterior wall repair is shown with upper levator muscle suture attached to cervical blocks. This is done only when a non-functional vagina is acceptable.

Comment

This plan for performing the vaginal hysterectomy for uterine prolapse is in a sense more related to the Spalding-Richardson⁶ composite operation than the other techniques we have used in that the essential ligaments for uterine support remain attached to strong fibrous cervical tissue. An advantage offered by the technique described here over the Spalding-Richardson operation is that the shortening of the cardinal and uterosacral ligaments can be carried out more extensively and more opportunity is afforded to deal with the important closure of the pouch of Douglas. In addition, none of the cervical canal or isthmic portion of the uterus is left in.

A procedure described by Kulshreshtha⁷ which he refers to as a modified Mayo-Richardson operation also leaves the lateral aspects of the cervix, but in addition the

lateral portions of the fundus are also preserved. After these two lateral halves of the uterus are united, the united mass is brought in front of the bladder and fixed on each side to the pubic arch much as is done in the Watkins transposition operation. In a sense this is more truly a modification of the Watkins operation.

The degree to which the operation described here will diminish our failures in the more severe degrees of prolapse is not known. We have not treated enough cases and the follow-up period is yet too short. It is not likely that the results could be worse than our present experience and there is the hope that they may be improved. The technique is presented for the gynecologic surgeon who is not entirely satisfied with his end results in this challenging group of cases and is ready to accept another version of the many modifications of the vaginal hysterectomy.

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Vaginal support and stress incontinence: a new approach

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DURING the past several decades, three major controversies have exploded the smooth surface of gynecologic thinking and changed forever the most basic concepts of gynecologic surgery. The first of these—total versus subtotal hysterectomy—has just been buried under a mound of series and a few bored editorial comments. The second—abdominal versus vaginal hysterectomy—still rages with undiminished vigor, neither side yielding an inch. The third—on the causes and treatment of stress incontinence—moves restlessly from anatomic unit to surgical theater where plausible theories continue to be disproved by a high level of failure in practice. Even the early work of Donald of Manchester and Kelly of Baltimore indicated that the most perfect vaginal repair which fails to relieve stress incontinence is a regrettable surgical error. Yet, from a survey of responsible series in the last 15 years, it is apparent that no ingenious method so far devised can guarantee satisfactory cure of this distressing symptom. For that reason, we are advancing here an entirely different, but much more unified, approach to the problem.

Historical review

Although the earliest attempt to treat stress incontinence as a surgical entity was recorded by Schultz¹ in 1878, the first serious efforts toward its cure were associated with the vaginal repair operation of Fothergill published 10 years later. It soon became apparent, however, that, although this operation achieved satisfactory results in most

cases, a disturbingly high percentage of failure and even aggravation of symptoms had yet to be explained. In 1913, Kelly² suggested plication of the urethral sphincter to improve these results, but his percentage of cure was little if any better than that of his English contemporary. To this day, the Fothergill or Manchester technique is still followed in the majority of English clinics and in many European and American centers as well. Its proponents argue, and with justice, that their cure rate is at least as high as that of most methods devised in the last two decades. It is also just as low—and therefore no excuse for complacency.

Concurrent with development of newer measures for its cure, attention became focused on the underlying mechanics of stress incontinence. Kennedy,³ a pioneer investigator in this field, concluded that fixation by scarring due to birth trauma rendered the sphincter incompetent and thus permitted stress emission of urine. He therefore attacked the problem surgically by freeing the sphincter and urethra from their lateral scar tissue attachments. Again, as with the Kelly technique, the failure rate varied between 10 and 20 per cent.

The next forward stride was the installation of a permanent "crutch" beneath the urethra. Aldridge,⁴ aware of the failure of previous techniques, concluded that not only should the sphincter lumen be reduced in size but that the urethra also needed adequate support to permit free sphincter action.

This led him to revive and modify the original Goebel-Stoeckel technique by in-

serting a sling of rectus fascia under the urethra. The band tightens with any increase in intra-abdominal pressure and so provides support when and where most needed. Such an operation demands of the operator the best judgment in assessing the supportive strength of available tissues, as well as an exact sense of the tensions to which they must be subjected. Weak fascia may ultimately become useless; yet such tissue inferiority is common in the very patient who needs this operation most. If the fascial strips are too loose, the sling is useless; if too tight, the patient may be able to void only in a half-crouching position. It is not surprising, therefore, that, as Jeffcoate⁵ comments, the results of this operation frequently deteriorate in time and that relapse may occur as late as 6 years or longer after operation. Further modifications of the sling operation include those of Studdiford⁶ and Millin and Read.⁷ Both are subject, in varying degrees, to the same errors basically inherent in all sling techniques.

In the late 1940's, attention began to concentrate on the causal relationship between descent of the bladder base, loss of the urethrovesical angle, and stress incontinence. The sling operations had already emphasized the importance of the second factor. The Marshall-Marchetti-Krantz operation⁸ considered both in attempting to correct this distressing symptom. By this method paired permanent sutures attached the paraurethral and urethral tissues to the periosteum behind the symphysis. This lifted the urethra snugly behind the symphysis, elevated the bladder base, and produced a sharp angulation at the urethrovesical junction. The operation was comparatively simple to perform and with it these workers obtained promising results where older methods of repair had failed. It moreover reduced variability of urethral support as in the sling operations to a much more predictable level. However, a grave, new factor was introduced—that of infection of the permanent sutures with resulting periostitis which, though rare, could be very disturbing.

This operation has never been suggested as a panacea and is advised by its authors, with becoming modesty, only when the usual repair techniques have been unsuccessful. The cure rate by the technique of Marshall, Marchetti, and Krantz has varied from 84 per cent⁹ to 85 per cent.¹⁰ During the last 10 years this method has gained in popularity over the sling technique for reasons apparent in the foregoing discussion. Yet it seems to have provided little improvement in cure rate.

The ticklish problem of stress incontinence has been broached from several other angles as well—one nonoperative, the others surgical. The first, advocated by Kegel,¹¹ consists of exercises designed to strengthen the atrophic muscles in the vesical neck. When performed three times a day for the prescribed 20 minutes, these have been claimed to result in cure or improvement in 81 per cent of cases of stress incontinence, a figure which almost equals current surgical results. His work has more recently been confirmed by Wharton,¹² who points out the complete dependence of urinary control upon the healthy contractility of the sphincter mechanism.

Among the more interesting of the recent surgical procedures is Mulvaney's operation of urethrovesicolysis.¹³ By rapid blunt dissection through a suprapubic incision, he freed the urethra, bladder neck, and bladder from their surrounding adhesions and claimed a perfect cure in all of 58 patients operated upon. Lennon,¹⁴ however, using his operation, felt that support from below was quite as necessary as mobilization. He obtained a cure rate of 92 per cent while Harper and Russell,¹⁵ following Mulvaney's technique more exactly, obtained complete cure of stress incontinence in only 80 per cent of their cases.

In 1958, Frankel¹⁶ reported a method for establishing the posterior urethrovesical angle by full thickness anterior colporrhaphy. This ingenious technique was successful in the small series reported. In developing his technique he aligned himself with Goff¹⁷ and others against belief in the presence of a true

pubocervical fascia. Impressive evidence for existence of the latter has, however, recently been reported.¹⁸

During the past two decades the direct attention focused upon the underlying mechanism of stress incontinence has helped to establish the basic pathology of the disorder. Marchetti,¹⁹ in 1949, Jeffcoate and Roberts⁵ in 1952, and Lund, Fullerton, and Tristan²⁰ in 1959, by extensive cystourethrography, have indicated that, to produce this symptom, several or all of the following defects must exist: (1) loss of the posterior urethrovesical angle; (2) funneling of the urethrovesical junction with a loss of this angle; (3) descent of the base of the bladder (it is noteworthy, however, that, if the urethral descent is proportional to that of the bladder base, the angle is maintained and no incontinence develops); (4) damage to the midurethral segment.

Other contributing factors associated with birth trauma include lack of support under the urethra and scarring of the urethral sphincter. To ensure successful treatment, all such causes must be carefully differentiated from those arising from lesions other than traumatic. These include congenital anomalies of the urinary tract—ectopic ureters, diverticula and strictures of the urethra, the so-called congenital valves in the proximal urethra and hypoplasia of the urethrovesical musculature. Less commonly, nerve lesions may develop—"cord bladder," *tabes dorsalis*, and cord tumors, to mention a few. Tumors, calculi, and hernias at the trigone may also contribute causally, while external factors, such as uterine, adnexal, or even bowel masses, may produce a picture almost identical with that of true stress incontinence.

In spite of widespread investigation to determine the causes of stress incontinence and the many ingenious procedures tailored to combat them, no method of treatment yet devised can be relied upon to cure more than 85 per cent of cases of stress incontinence. A final answer to the problem, therefore, must provide simultaneous and permanent cure for the most basic causes

of the condition and should effect an adequate restoration of the vagina as well.

Achievement of such a result has been the object of my search during the past 13 years. Having received part of my graduate training under the late Dr. N. Sproat Heaney, it was inevitable that my first approach to the problem should be through vaginal hysterectomy and repair. However, for reasons advanced and examined below, this method was reluctantly abandoned for the combined technique of vaginal repair and total abdominal hysterectomy. The latter, as will be shown, has produced incomparably better results both in supporting the vagina and in curing stress incontinence.

Materials

The present report is based on a series of 511 consecutive unselected cases comprised entirely of private patients operated upon during the 12 year period from 1948 to 1960. The series was collected, examined, and carefully analyzed by a disinterested gynecologist, Dr. Z. Walko, to obviate the least possibility of sympathetic interpretation of results. Since the inherent weakness of so many astronomical series compiled by hospital and University groups is the wide diversity of surgical skills and criteria existing among contributors, it was felt that the unified approach of a completely personal series was of some importance. Indeed it is probable that a comparison between major techniques can be assessed accurately only when both are performed by a single pair of hands and judged impartially by one set of criteria.

Our first group was composed of 85 patients treated by complete vaginal repair with vaginal hysterectomy. In the second series of 426 cases the technique was that of vaginal repair with total abdominal hysterectomy. In none of the cases reported was subtotal hysterectomy considered since the greater value of the total procedure has been established beyond question.

Technique

The techniques of vaginal hysterectomy employed in the first series were of the usual

types—the standard Mayo operation and Heaney's technique—with minor modifications. Both have been thoroughly described elsewhere and need no further comment here.

Our combined technique of extensive vaginal repair and total abdominal hysterectomy will be described in detail, however, since its results are the most significant contribution of this paper. The operation includes the following steps:

1. Vaginal repair. Vaginal repair is always performed first, since a sufficiently wide separation of fascia from the anterior vaginal mucosa is almost impossible without firm downward traction upon the cervix during the procedure. The exact relationship of bladder to cervix should first be verified by the insertion of a uterine sound into the bladder as the level of their attachment is highly variable.

A transverse incision is made in front of the cervix, immediately below the vesicocervical fold. The vaginal mucosa and fascia are dissected from the bladder in the midline by tunneling with curved scissors through the correct plane of cleavage as high as the urethral meatus; then the mucosa is incised in the midline. Starting at the meatus, the fascia is divided by the scalpel parallel to the cut edge of each flap and its separation continued by blunt dissection as far laterally as possible on both sides. The bladder is then freed by blunt dissection from its attachments to the cervix. A Foley catheter is next inserted and its bag inflated.

Starting at the level of the meatus, the fascia on either side of the urethra is united firmly beneath it with mattress sutures as far as the urethrovesical sphincter. The location of this sphincter is established by traction upon the catheter and palpation of its bag.

The strong subvesical and vaginal fascia is then apposed with further mattress sutures below the bladder as firmly as the tissues will permit. Since the attenuated fascia immediately beneath the herniated bladder is capable of little support, it is vital that each suture be inserted as far laterally as possible

to pick up the tough fascia so long retracted to that position. The first of these stitches, however, is placed not less than one inch posterior to the last suture at the urethrovesical junction. The simple expedient of leaving a "strategic gap" between the firmly supported urethral sphincter anteriorly and the firmly supported bladder posteriorly produces a functionally acute urethrovesical angle on straining movements (Fig. 1). Thus, the first major measure in the prevention of stress incontinence is achieved.

When the subvesical fascia has been sutured as high as possible to establish, yet not constrict, the vault, the excess vaginal mucosa is excised and the flaps united with interrupted mattress sutures, each catching a bite of the fascial layer to obliterate dead space.

A similar transverse incision is made at the fourchette, and the vaginal wall and rectum separated by burrowing with curved scissors to the upper limit of the existing rectocele. The mucosa is incised and separated from the fascia as in the anterior repair. If the rectocele is high, as it so often is, the upper fascia is repaired by a purse-string suture to prevent constriction of the vault. Below this, the fascia is tightened with mattress sutures as low as the levators. The latter are united with two deep sutures, the second including the perineum. The excess mucosa is excised, and the flaps apposed with interrupted sutures. The bladder is emptied and the vagina packed with 2 inch gauze, to be removed just as the uterus is excised.

2. Total abdominal hysterectomy. The abdomen is carefully prepared and opened. Since the combined operation is extensive, it is imperative that the technique of hysterectomy be safe, rapid, and as simple as possible. The uterus is first separated from any adhesions and grasped firmly. I have found the use of a tumor screw to be admirable for this purpose. It permits adequate traction and complete mobility of the organ during subsequent procedures. If the adnexa are to be removed, the round and infundibulopelvic ligaments, otherwise the round and ovarian ligaments, are securely sewn with the Heaney

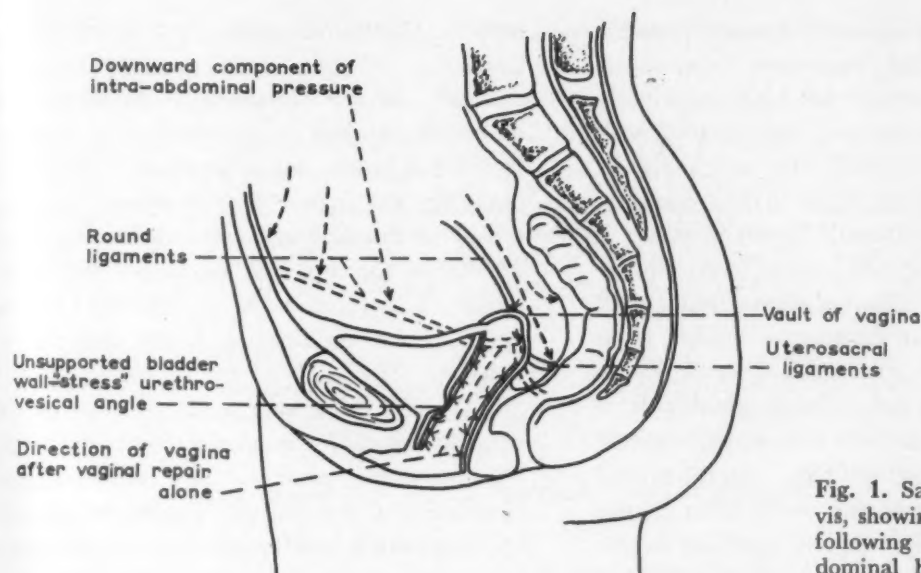


Fig. 1. Sagittal section of pelvis, showing direction of vagina following repair and total abdominal hysterectomy.

stitch, and the sutures left long. The round, ovarian, and upper portions of the broad ligaments are next clamped close to the uterus with Kocher forceps to prevent reflux bleeding. The adnexa are separated distal to the sutures and divided from the uterus or removed with it, depending on whether or not they are to be retained.

The bladder reflection of peritoneum is separated from the anterior uterine wall with curved scissors between the round ligaments and reflected downward, separating

the bladder from the lower uterus and cervix. To suture the uterine vessels, the needle is inserted immediately lateral to the uterosacral ligament posteriorly, emerges close to the cervix anteriorly, and is completed with a second loop through the pedicle as a Heaney stitch. As each suture is tied, the Kocher forceps on the corresponding side of the uterus become useless and are removed. The ligated uterine vessels are divided from the uterus with scissors and retied with the same sutures for greater security.

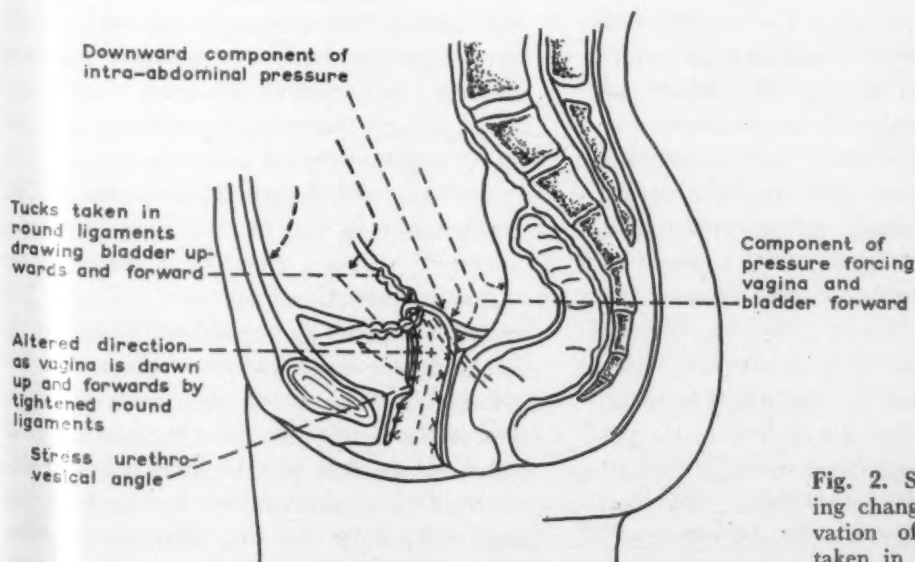


Fig. 2. Sagittal section showing changed direction and elevation of vagina with tucks taken in round ligaments.

The uterosacral ligaments are next sutured and cut. Then the transverse cervical or Mackenrodt's ligaments are clamped closely parallel to the cervix, cut, and ligated with a Heaney stitch. (This is the only occasion during the operation when tissues are first clamped before ligation.) Now the pelvis is free of forceps and the uterus held only by the tumor screw. The anterior vaginal wall is next incised and the uterus divided from the vagina with curved scissors as closely as possible to the cervix. The vaginal cuff is then grasped by Kocher forceps at strategic points—each anterior flap, each lateral angle, and a fifth at the midportion of the posterior wall. The vaginal packing is removed. The vault and cut edges of the vagina are swabbed with benzalkonium, and a suture placed uniting the two anterior flaps with the pubocervical fascia at the height of the vagina. This suture is left long for traction and cut only as the vault is closed.

Angle sutures are then placed by means of the TeLinde technique—through uterosacral ligament, posterior vaginal wall, out through the lateral wall transfixing the transverse cervical ligament, back through the vaginal wall anterolaterally, and out anteriorly through the vaginal wall and pubocervical ligament. When each angle suture is tied, it controls all angle bleeding and secures to each corner the uterosacral, transverse cervical, and pubocervical ligaments. These sutures are left long. The vaginal vault is next closed between the two angle sutures with a continuous suture. The round and ovarian ligaments, if the ovaries are to remain, otherwise the round and infundibulopelvic ligaments, are sutured to the vaginal vault with each angle suture, tucks being taken in the round ligaments to suspend the vagina still more firmly and give it the greatest possible length (Fig. 2). By this means, the whole bladder is also lifted strongly upward and forward. It is thus supported by repaired vesicovaginal fascia posteriorly and the tightened round ligaments superiorly. The vaginal stump is next peritonized completely, the appendix removed if advisable, and the abdomen closed in six

layers (continuous and interrupted in the fascia).

Much of the foregoing description will, of course, appear unnecessary to a surgeon in the full bloom of his experience. However, omission of many details considered too trivial to describe can often create very real difficulties for someone learning a new technique. For those who prefer still further detail, these additional hints may prove helpful:

1. It is a fact known to all experienced surgeons that the tensile strength of tissues is never the same in any two patients. Shredding of the vaginal mucosa, when held by Allis or Kocher forceps may be prevented very effectively by grasping it parallel to the cut edge with a hemostat and moving the latter along as required during blunt dissection.

2. In spite of the greater speed of sharp dissection, it is bloodier and less accurate in defining planes of cleavage than blunt separation. A judicious combination of both as described above would appear to be the method of choice.

3. In extensive anterior repair, it is important to check the vault as the last sutures are placed. It is almost as easy to constrict a vaginal vault anteriorly as it is posteriorly.

4. In older patients, an apparently relaxed vault may become a senile, contracted one when repair is completed. To prevent this defect, looser sutures are taken at this level. Age and widowhood are no guarantee against the ardors of a second marriage. It is a primary purpose of repair to see that every vagina remains functional.

5. Since the extent of a rectocele, and particularly its height, are never the same in any 2 patients, these facts should be accurately predetermined and treated individually—never by any rule-of-thumb wedge excision, or perfunctory suture of the thinned-out fascia at the mucosal edges. Rectocele repair may have little or no effect upon subsequent rectal function but it does provide vital support to the vaginal vault and defines its eventual dimensions. When the mucosa at the vault is scanty, yet the

Table I. Pelvic pathology and vaginal relaxation without stress incontinence (Series I, 32 cases)

Major indications for operation	No. of operations	Major complications	Results					Mortality
			Six weeks' examination	Sequelae		Follow-up examination	%	
				Type	Treatment			
Pelvic pathology	16	Secondary hemorrhage, 1	Support of vault, good 29; poor 3	Urethritis and vaginitis, 14	Antibiotic treatment of moniliasis and trichomonas infection	Support good, 29	90.6	1 (3.1%)
		Thrombocytopenic purpura, 1	Short vagina, 2		Painting of urethra and vagina with 1/2% gentian violet	Support poor, 3	9.4	Thrombocytopenic purpura on eighth day
Prolapse	10		Cystocele, 4			Short vagina, 2	6.2	
						Cystocele, 4	12.5	
Urethro-cystocele and rectocele	6	Carcinoma in situ, 1		Enterocoele, 2	Repair of enterocoele	Rectocele, 3	9.4	
		Carcinoma of uterus, 1	Rectocele, 3	Carcinoma of uterus	Deep x-ray therapy for carcinoma	Frequency, 1	3.1	
			Frequency, 1			Poor control, 1	3.1	
			Poor control, 1			Poor control, 1	3.1	
			Stress incontinence, 0			Stress incontinence, 1	3.1	

fascial defect extends much higher, separation of the fascia can be extended by tunneling under the mucosa as far as necessary. The fascia, so mobilized, may then be repaired by a purse-string suture without decreasing the size of the vault. When uniting the mucosal flaps, the sutures should not catch underlying fascia until they are low enough so as not to constrict the vault.

6. Every patient with a high rectocele should be examined to rule out the possibility of an enterocoele. Any tendency in this direction can be obviated by obliteration of the cul-de-sac abdominally, after completion of hysterectomy, by means of a simple purse-string suture technique.

7. In the method of abdominal hysterectomy suggested above, all tissues are treated by primary suture without first clamping and dividing, as in the usual techniques. The only exception to this is when the transverse cervical ligament is clamped before suture to prevent damage to ureters. The advantages of this method are apparent. When sutures are inserted directly without previous

clamping of tissues, they have a better purchase and are less apt to slip. Also, there is the least possible amount of "hardware" in the pelvis at any time. This is especially important when fat, a deep pelvis, or other causes increase the difficulty of access. Since exposure is thus improved, the operation becomes easier and is more rapidly performed.

8. The combined vaginal repair and total abdominal hysterectomy is performed in an average time of between 1 hour and 45 minutes and 2 hours, depending on the difficulty of the case. It has been completed in 1 hour and 30 minutes in uncomplicated cases. The times cited include the interval for change-over between the vaginal and abdominal parts of the operation. No. 1 chromic catgut is used throughout both vaginal repair and abdominal hysterectomy.

Results

Tables I and II record the results in 85 cases where pelvic pathology and vaginal relaxation were treated by vaginal hysterectomy.

Table II. Pelvic pathology and vaginal relaxation with stress incontinence
(Series I, 53 cases)

Major indications for operation	No. of operations	Major complications	Results					Mortality
			Six weeks' examination	Sequelae		Follow-up examination	%	
				Type	Treatment			
Pelvic pathology	19	0	Support of vault, good 49; poor 4	Urethritis and vaginitis, 28	Antibiotic treatment of moniliasis and trichomonas infections	Support good, 50	94.3	0
Urethro-cystocele and rectocele	20					Support poor, 3	5.7	
Prolapse	14		Short vagina, 3		Painting of urethra and vagina with 1/2% gentian violet	Short vagina, 3	5.7	
			Cystocele, 2			Cystocele, 4	7.4	
			Rectocele, 2	Enterocoele	Repair of enterocele	Rectocele, 3	5.7	
			Frequency, 2			Frequency, 4	7.4	
			Poor control, 1			Poor control, 1	1.9	
			Stress incontinence, 1			Stress incontinence, 1	9.4	

Table III. Pelvic pathology and vaginal relaxation without stress incontinence
(Series II, 188 cases)

Major indications for operation	No. of operations	Major complications	Results					Mortality
			Six weeks' examination	Sequelae		Follow-up examination	%	
				Type	Treatment			
Pelvic pathology	128	Cardiac disease, 2	Support of vault, good 188; poor 0	Urethritis and vaginitis, 103	Antibiotic treatment of moniliasis and trichomonas infections	Support good, 188	100	1 patient 0.6% of cardiac disease on eighth postoperative day
Urethro-cystocele and rectocele	40	Vesico vaginal fistulae, 1	Short vagina, 0		Painting of urethra and vagina with 1/2% gentian violet	Short vagina, 0	0	
Prolapse	20	Cystocele, 2		Vesico-vaginal fistula, 1		Cystocele, 2	1.06	
		Carcinoma in situ, 1	Rectocele, 1	Carcinoma in situ, 1	Repair of vesicovaginal fistula, good result	Rectocele, 1	0.6	
		Early carcinoma of cervix, 1	Frequency, 16	Carcinoma of cervix, 1		Frequency, 3	1.6	
		Carcinoma of ovary, 1	Poor control, 6	Carcinoma of ovary, 1	Deep x-ray therapy for carcinoma	Poor control, 3	1.6	
		Secondary hemorrhage, 2	Stress incontinence, 2	Ureteral obstruction	(later) Transplantation of ureter into bladder result—good	Stress incontinence, 2	1.06	
		Ligation of one ureter						

tomy and repair. Tables III and IV record the results in a series of 486 cases with similar indications but where treatment consisted of vaginal repair and total abdominal hysterectomy. In the first series, 53 patients suffered from stress incontinence varying from moderate to severe; in the second, 238 were similarly afflicted—roughly, the same proportion. The great majority of the patients with stress incontinence had been delivered before obstetrics became more carefully controlled in this area. In the last 10 years there has been a marked improvement in the standard of obstetrical practice generally. It is, therefore, virtually certain that such a series with stress incontinence may not again be available to us for study and treatment.

Age incidence and mortality. The age spreads in both series (Table V) were remarkably similar. In the first group, treated with vaginal hysterectomy and repair, the youngest patient was 29 years old and the oldest 82, while in the second, where repair was combined with abdominal hysterectomy, the youngest patient was 28 and the oldest 79 years of age. As shown in Table V, the majority of patients were operated upon when between 31 and 60 years of age—83.4 per cent in Series I and 92.4 per cent in Series II. Of these, almost half were within the 41 to 50 year age bracket. In both series several had had previous coronary and other heart lesions, yet developed no complication during convalescence. This is due, we suspect, to the routine use of adequate vitamin E therapy postoperatively. A significant percentage of patients in the elder group of both series were hypertensive. Moreover, most patients in both groups were overweight since the association of obesity with tissue inferiority is a common observation.

In spite of this wide range of age incidence, previous cardiac and metabolic defects, and occasionally the grave operative menace imposed by obesity, there were no immediately operative deaths in either series. In the first group, one patient died on the eighth postoperative day from hemor-

rhages produced by previously undiagnosed thrombocytopenic purpura. Of the second group, treated by vaginal repair and abdominal hysterectomy, 3 patients died—2 of heart failure on the eighth and eleventh days, respectively. The third developed dehiscence of the upper end of the wound on the eighth day and died from cardiac arrest one hour after its repair. In the series of 85 patients treated by repair and vaginal hysterectomy, the death rate was 1.2 per cent, while in the group of 426 patients treated with vaginal repair and total abdominal hysterectomy the mortality was 0.73 per cent. It is of interest that of these patients none died before the eighth postoperative day and all succumbed to associated organic defects not traceable to the operation.

Support of vagina. Comparative analyses of results in the two series treated by these differing methods lead to certain inescapable conclusions. Support of the vaginal vault following vaginal hysterectomy and repair was excellent in all but 6, or 7.1 per cent, of the 85 cases in Series I. An enterocele had recurred in 3 of these cases. In Series II, on the contrary, vaginal vault support was excellent throughout with the exception of 2 cases of enterocele—a failure rate of 0.5 per cent. Five short vaginas (2 to 2½ inches deep) resulted in Series I; in the second series there was none. Cystocele of moderate degree recurred in 8 and rectocele in 7 of the 85 cases in Group I, as against 4 recurrent cystoceles and 1 rectocele among the 426 cases in Group II. The recurrence of enterocele following vaginal hysterectomy in Series I is of the same order of frequency as in previously reported series, 3 among 85 cases. By contrast, the almost complete absence of this vault defect in 426 cases treated by vaginal repair and total abdominal hysterectomy is highly significant.

Depth of vagina. An attempt was made to measure the vaginal depth achieved by both types of operation. In patients treated with vaginal hysterectomy and repair this varied from 2 to 3½ inches with an average depth of 3¼ inches. By contrast, the vaginas of

patients in Group II, who had been treated with vaginal repair and total abdominal hysterectomy, varied between $3\frac{1}{4}$ and 5 inches long, averaging 4 inches. Clearly, therefore, the latter technique produced deeper and more adequate vaginas. In this group, also, a stronger vault resulted, with notably less tendency toward formation of an enterocele. In many of these cases, the vaginas are actually deeper after operation because of inclusion of the cuff and the tight upward support of the shortened round ligaments.

Cure of stress incontinence. Comparison in respect to the above factors, though significant, is of less importance than the improvement in control of stress incontinence shown by the second operation (Table VI).

In Series I, out of 53 cases with the symptom previously, operation failed to effect a cure in 5 cases or 9.4 per cent (Table II). In this group, one further patient who did not have this symptom previously developed it after operation (Table I).

In Group II, of 238 cases with previous stress incontinence, operation failed to cure 5 patients or 1.7 per cent (Table IV). Two patients without stress incontinence developed the symptom after operation (Table III).

In both series, a small number of patients continued to complain of "urinary insecurity," after all vaginitis and urethritis was eliminated by antibiotic therapy and treatment of Monilia and Trichomonas infec-

Table IV. Pelvic pathology and vaginal relaxation with stress incontinence (Series II, 238 cases)

Major indications for operation	No. of operations	Major complications	Results					Mortality
			Six weeks' examination	Sequelae		Follow-up examination	% 100	
				Type	Treatment			
Pelvic pathology	84	Cardiac disease, 1	Support of vault, good 238, poor 0	Urethritis and vaginitis, 127	Antibiotic treatment of moniliasis and trichomonas infection	Support good, 238	100	2 (0.84%)
Urethro-cystocele and rectocele	126	Severed ureter, 1	Short vagina, 0		Painting of urethra and vagina with ½% gentian violet	Support poor, 0	0	1 died of cardiac disease on the eleventh postoperative day
Prolapse	28	Secondary hemorrhage, 2	Cystocele, 2			Short vagina, 0	0	
			Rectocele, 0	Carcinoma of uterus, 1	Deep x-ray therapy for carcinoma	Cystocele, 2	0.84	1 died of cardiac arrest one hour after repair of evisceration
		Carcinoma of uterus, 1				Rectocele, 0	0	
				Leiomyosarcoma		Frequency, 6	2.5	
		Leiomyosarcoma, 1	Frequency, 18					
			Poor control, 3	Evisceration, 1	Repair of evisceration	Poor control, 3	1.3	
			Stress incontinence, 2	Partial obstruction, 2	Separation of adhesions	Stress incontinence, 4 (very mild)	1.68	
				Severed ureter	Re-implantation of ureter into bladder result—excellent	Enterocoele, 2	0.84	
						Fair control, 2	0.84	

Table V. Age distribution of patients in Series I and II

Operation performed	21-30	31-40	41-50	51-60	61-70	71-80	Over 80	Percentage
Vaginal repair and vaginal hysterectomy	With stress incontinence	2	8	24	11	6	1	41-50 = 45.3 31-60 = 80.1
	Total series	2	21	33	17	10	1	41-50 = 38.8 31-60 = 82.4
Vaginal repair and total abdominal hysterectomy	With stress incontinence	1	62	112	46	13	4	41-50 = 47.1 31-60 = 92.4
	Total series	3	133	180	80	22	8	41-50 = 42.2 31-60 = 92.2

tions. These were classified under the heading, "poor control of urine," while those who still exhibited stress incontinence were included in the latter classification as well.

Vesicovaginal fistula. One such complication occurred in a patient in Series II with extensive endometriosis at the base of the bladder. It was recognized only on the eighth day, when the patient began passing urine per vaginam. It was apparent that separation of the vagina from the bladder had interfered with the blood supply to this area of bladder wall with subsequent necrosis. The patient recovered completely after repair of the fistula and has been well for the 3 years since the operation.

Ureteral damage. In 2 cases of Series II, a ureter was damaged during operation. In one patient who had had a previous vaginal repair, the ureter had been deviated medially by fibrous tissue and appeared to arise from the middle of the bladder fundus. During dissection of the latter from the cervix it was severed. Fortunately, the error was recognized at once and the ureter immediately reimplanted into the bladder. Subsequent convalescence was without incident.

In the second instance, where the patient had been very recently pregnant, the ureter was lying directly beside the cervix and was inadvertently sutured during operation. The accident was soon discovered, and the ureter was reimplanted into the bladder 8 days later. As in the previous case, the result of transplantation was excellent.

Secondary hemorrhage. Secondary hemor-

rhages were few in both series. They were treated expectantly in all but one case. In this patient, repeated hemorrhages forced reopening of the abdomen and secondary suturing of the bleeding vessel on the fifteenth day. The patient developed acute peritonitis subsequently, but recovered without further incident.

Treatment of malignancy. Cases of carcinoma discovered incidentally at operation were treated postoperatively with deep x-ray and cobalt therapy where these were indicated. The cases of carcinoma in situ required no further treatment. All patients with carcinoma in both series including one with leiomyosarcoma are alive and apparently well at the time of this writing. These include a patient with advanced bilateral ovarian carcinoma who was operated upon 4 years ago. A local recurrence in this case has recently required further x-ray therapy.

Follow-up examination. Follow-up examinations were possible in all but 66 of the 511 patients in both series. The larger number of this group were referred patients who were examined at the sixth week and then returned to their private physicians for further observation and care.

Comment

In both the above series treated by two widely differing techniques, there was a wide age-spread between the youngest (29 years with the vaginal and 28 with the abdominal hysterectomy) and the oldest patient (82 years in Group I and 79 in Group II). All

age groups appeared to bear the brunt of the combined operation equally well, indeed with no more apparent distress than either a repair or hysterectomy alone would have occasioned. As indicated in Table V, 81.2 per cent of patients in the first series and 92.1 per cent in the second series lay within the age range of 31 to 60 years, figures which agree fairly closely with those in other series.

The problem of operative risk in 2 such extensive procedures is of extreme interest, and one on which the 2 series throw considerable light. Though the first group treated by the vaginal approach only is much smaller than the second, the mortality was very similar. In neither series did any patient succumb during or immediately after operation. All deaths occurred at least 8 days post-operatively, and all but one from cardiac complications. Two of these patients had been up and about for days before the complications supervened—in one case cardiac failure and in the other, partial wound dehiscence. In the vaginal hysterectomy series, the patient who died had been suffering from unrecognized thrombocytopenic purpura and developed an acute hemorrhagic exacerbation of the disease several days postoperatively. It would appear, therefore, that a mortality of 1.2 per cent in Series I and 0.71 per cent in Series II, where no fatality occurred during or immediately after operation, argues strongly for the great and equal safety of both operative techniques.

Certain features of technique in combined vaginal repair and total abdominal hysterectomy are so important that they merit restatement. Separation of the anterior vaginal fascia should be as extensive as possible. Then its thickest, laterally retracted portions are sewn firmly under the urethra and bladder, leaving an unsupported gap in the fascia one inch long posterior to the urethral sphincter. When abdominal pressure suddenly increases, the bladder wall in the unsupported gap beyond the sphincter sags instantly and forms a "stress" urethrovesical angle. Thus, very simply, the first factor in the cure of stress incontinence is provided.

Tight fascial repair of the vagina gives as much support to the bladder and rectum as can be achieved.

When total abdominal hysterectomy is then performed, care is taken to separate the vagina as close to the cervix as possible to preserve the additional length of the cuff. Now the ligaments previously attached to the uterus are transferred to the support of the vagina. Last of all, the round ligaments are sutured to the vault and, when tucks are taken in these, they lift the vagina firmly up and forward, deepening it maximally. Simultaneously, the repaired anterior vaginal wall and base of the bladder are also lifted as high as possible and brought sharply forward. This adds the second, and probably most important, factor in the restoration of urinary continence—elevation of the base of the bladder.

Now, when intra-abdominal tension is suddenly increased, all downward pressure is exerted *behind* the bladder rather than *upon* it. The base remains high and unaffected, and complete continence is maintained.

On the contrary, where vaginal hysterectomy has been performed, the bladder, lying upon the shelf of the united broad ligaments, is exposed directly to the full force of downward pressure. The bladder base descends, the urethrovesical angle straightens out, and stress incontinence results. It is not surprising, therefore, that this defect may develop after the most careful vaginal hysterectomy and repair. Theoretically and practically, it should occur much more often.

Thus, combined vaginal repair and total abdominal hysterectomy should result not only in a deeper and more useful vagina, but also in a much higher cure rate for stress incontinence than achieved by vaginal hysterectomy and repair, or any other current method. This impression seems to be borne out by the facts (Table VI). As Eastman states in a recent editorial comment on the subject,²¹ "Of greater interest is the fact that the over-all end results were in the general neighborhood of the conventional 85%." In our series, combined vaginal repair and total abdominal hysterectomy has produced

a cure rate of 98.3 per cent for this urinary symptom. In addition we secure a vagina which is deep, well supported, and functional.

The results in patients treated with repair and subtotal hysterectomy have not been encouraging. Not only is the retained cervix a potential of future danger, but it prevents really effective deepening of the vagina and elevation of the bladder base. Unfortunately, its supportive role in reparative pelvic operations has been greatly overstressed.

Another factor of some importance, though of lesser interest, is the comparatively low rate of recurrence of enterocele after vaginal repair and total abdominal hysterectomy (2 in 426 cases). Several factors contribute to this: high elevation of the vagina following total hysterectomy, better support to the vault than is obtainable by other means, tightening of the uterosacral ligaments under direct vision, and, where indicated, obliteration of a deep cul-de-sac by purse-string sutures—all play a part in attaining this result.

When a patient reports with frequency and/or poor control and stress incontinence, it has been my practice during the last 10 years to paint the vagina and urethral canal with 1/2 per cent aqueous gentian violet for 4 to 5 weekly treatments to remove any urethral infection. The results of this work will be published at a later date. By this means, frequency and poor urinary control are often cured completely, or at least greatly alleviated. Moreover the procedure helps to differentiate stress incontinence due to local infection inhibiting the sphincter mechanism from that of traumatic or other mechanical origin. Thus, patients unimproved after thor-

ough trial of this treatment have an excellent chance of cure by surgical methods.

The method suggested for treating the urethral canal is merely to impregnate cotton narrowly wound on an applicator stick with 1/2 per cent aqueous gentian violet and insert it slowly and gently into the urethra to a point just beyond the internal sphincter. The patient is then asked to tighten and relax the levators and gluteal muscles alternately three or four times. This allows the stain to enter the paraurethral glands where infection is mainly resident. The vagina is then painted in the usual way.

As indicated previously, we have been able to cure a great many patients with poor urinary control, frequency, and stress incontinence who would otherwise have been treated surgically. Urethritis may recur several times in any patient, either before or after operation. Indeed, many excellent operative results may appear to have failed because of incontinence from urethral infection. The use and, if necessary, repetition of this direct treatment of the urethra not only solves the problem of when to operate but can also resolve a dubious operative result into a permanent success.

It has recently been pointed out that in vaginal repair many an apparent surgical success may be followed by varying degrees of marital failure. In an attempt to evaluate this vital human factor in my own series, I discussed with as many patients as possible their reactions to marital experience after operation. The replies were surprisingly frank and factual. In the younger group—45 years and under—the great majority enjoyed relations at least as much as before, provided they had previously done so. Of

Table VI. Results in treatment of stress incontinence in Series I and II

Type of operation	No. of operations	Cases without previous stress incontinence		Cases with previous stress incontinence		Total cases free from stress incontinence postoperatively
		No.	Postoperative incontinence	No.	Postoperative incontinence	
Vaginal repair and vaginal hysterectomy	85	32	1 (3.1%)	53	5 = 9.4%	78 (92.9%)
Vaginal repair and total abdominal hysterectomy	426	188	2 (1.06%)	238	4 = 1.68%	420 (98.5%)

those with great vaginal relaxation prior to operation, the majority found sexual life more interesting than it had been for years. Psychological factors, however, entered strongly into the sexual response of this group. Relief from the fear of pregnancy was a great stimulus to normal activity in many. Continuing dissatisfaction with marriage or distaste for the marital partner, however, prevented normal readjustment in a smaller percentage of cases.

In the older group where experience had been infrequent or the husband ineffective prior to operation, the same response continued. A definite number in this age group, however, showed increased impatience with marital inaction after operation and admitted greatly increased libido. Where marital life had been active and satisfactory before operation in this group it usually continued to be so. The reaction of all age groups, therefore, appeared to indicate that when operation was properly performed, leaving a deep and painless vagina, the enjoyment of marital life was enhanced, if all psychological conflict had been resolved.

In view of the incidental findings of cervical carcinoma in situ in 2 patients, early invasive carcinoma of the cervix in one, carcinoma of the fundus in 2, advanced carcinoma of the ovaries in 1, and leiomyosarcoma in 1 patient—a total of 7 in 511 cases, or 1.4 per cent—the combination of total hysterectomy with repair has distinct value as a preventive measure. If this number be equated against 4 deaths from unrelated causes in the same series, the value of the dual approach is the more evident. It is my view, considering the quality of anatomical and functional results obtainable by this method, that whenever hysterectomy is indicated any necessary vaginal repair should be performed at the same time. Otherwise repair performed later becomes more difficult and less adequate and may reasonably raise a question at subsequent examination as to why primary surgical treatment had been left unfinished.

Conversely, also, when vaginal repair is really indicated for relaxation and its asso-

ciated symptoms the results of the combined technique are so superior to those of repair alone that it should be invoked in the interest of permanent cure unless some very real contraindication exists. Since combined vaginal repair and total abdominal hysterectomy appear to be the most effective answer to all problems of pelvic relaxation, I have reluctantly but permanently abandoned vaginal hysterectomy and repair in favor of this more satisfactory technique.

Conclusions

It appears from analysis of all available data in the two series reported above that the combined operation of vaginal and total abdominal hysterectomy is a safe procedure and applicable to patients in all age groups. It is at least as safe immediately and ultimately as vaginal hysterectomy and repair. There were no immediate operative deaths in either series.

It produces a much deeper vagina than vaginal hysterectomy and repair, with significantly less recurrence of cystocele and rectocele, and of enterocele. It provides a cure rate in stress incontinence of 98.3 per cent, as against 90.6 per cent with vaginal hysterectomy and repair, and an average of 85 per cent by all other methods.

The incidence of postoperative complications is no greater after this operation than with any other vaginal operation.

The greater latitude of the abdominal approach makes this operation more elastic for the diagnosis and eradication of concurrent abdominal and pelvic pathologic conditions than vaginal hysterectomy and repair.

Comparison of operations. Comparison of the Marshall-Marchetti-Krantz operation and various sling procedures with the techniques of combined vaginal repair and total abdominal hysterectomy suggests the following conclusions:

1. **Urethral support.** This is achieved in the Marchetti technique by firm urethral suspension to the symphyseal periosteum. In the sling operation, a fascial strap supports it. In the combined operation, the urethra rests on firmly repaired fascia.

2. *Urethrovesical angle.* All three methods provide an acute urethrovesical angle. The Marchetti procedure does this by permanent suture of the urethra to the periosteum behind the symphysis. The sling operations form a firm fascial support beneath the urethra. The combined technique as described above achieves it much more simply by leaving a "strategic gap" of unsupported bladder wall behind the vesical sphincter.

3. *Elevation of the bladder base.* In the Marshall-Marchetti method, the bladder is elevated by permanent suture of para-urethral and urethral tissues to periosteum—mobile to fixed tissues. Implicit in this method are the dangers of periostitis, possible "cutting-through" of the permanent holding sutures, and failure of firm union between tissues of dissimilar origin and tension. The sling procedure, which rests its case upon the urethrovesical angle alone, makes no attempt to elevate the bladder base. The combined technique, however, not only gives the bladder firm fascial support from below, but, by taking tucks in the round ligaments sutured to the vault, it lifts the repaired vaginal wall and bladder base as high as possible upward and forward. Healing is more dependable also since all the tissues united are completely mobile.

4. *Exposure of bladder to abdominal pressure.* In both the Marshall-Marchetti and the sling techniques, as well as where vaginal hysterectomy has been performed, the bladder is directly exposed to downward pressure from any intra-abdominal stress. With our method of combined repair and total abdominal hysterectomy, the bladder is elevated and brought sharply forward. It is thus shielded from the direct downward thrust which is then exerted behind it. Since

such intra-abdominal stress is exerted equally in all directions, its anterior component tends to force the bladder still farther forward and so actually helps to maintain its high level.

The problem of direct exposure of the bladder to the downward component of intra-abdominal pressure is a problem not sufficiently considered in the literature up to this time. It may yet prove the one most crucial factor in the failure of so many operations designed for the cure of stress incontinence.

Summary

1. The history of the surgical approach to the treatment of stress incontinence is briefly discussed.

2. Operative experiences are compared between the use of vaginal repair and vaginal hysterectomy and vaginal repair and total abdominal hysterectomy in 511 consecutive unselected cases from my private practice during the last 12 years.

3. The technique of vaginal repair and total abdominal hysterectomy is described in detail, with special emphasis upon the formation of a "stress" urethrovesical angle, and the highest possible elevation of the bladder base.

4. The results in two series, one with vaginal repair and vaginal hysterectomy, the other with vaginal repair and total abdominal hysterectomy, are tabulated and compared.

5. The results in these two series are discussed in detail, indicating clearly their comparative success in control of stress incontinence—90.6 per cent cure with vaginal repair and vaginal hysterectomy, 98.3 per cent with vaginal repair and total abdominal hysterectomy.

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Blood loss in vaginal operations and the use of preoperative intravenous estrogen

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Loss of major quantities of blood during vaginal-pelvic operations particularly in vaginal plastic procedures, has always seriously concerned surgeons. While concentration on the ligation of larger arteries and veins enables the operator to proceed with reasonable dispatch, troublesome venous plexus bleeding defies almost all efforts of control. Buchman¹ and Wexter² along with others have demonstrated the magnitude of blood loss during vaginal operations and note its gravity in good as well as in patients considered poor surgical risks.

Various methods known to produce local hemostasis have been employed but remain largely unsatisfactory. Dillon and associates³ reported a decrease in blood loss with vasopressin in myomectomy. Prompt cessation of hemorrhage after intravenous administration of 20 mg. of estrogen was observed by Jacobson.⁴ He noted along with various investigators^{5, 6} its value in diminishing bleeding associated with urological and gastrointestinal operations, tonsillectomy, adenoidectomy, and epistaxis.

Johnson⁷ experimentally illustrated in dogs that after the intravenous injection of 10 mg. of estrogen, the plasma level of accelerator activity is inhibited. Owren pointed out that accelerator globulin has an enormous influence on the velocity of thrombin formation.⁸

Considering the reported effective use of

intravenous estrogen in the control of blood loss, the following investigation was instituted.

Material and methods

One hundred patients, 68 of whom were being prepared for vaginal hysterectomy and 32 for vaginal hysterectomy with anterior and posterior repair, received 20 mg. of conjugated estrogens, equine (Premarin,* intravenous), one hour prior to operations. One hundred women, 71 of whom were being prepared for vaginal hysterectomy and 29 for vaginal hysterectomy with anterior and posterior repair, received no preoperative estrogen and were used as controls. The ages of these women ranged from 34 to 76 years. They were divided into 4 age groups. Blood loss during the operations was determined in each case.

Measurement of total blood loss was carried out in the following manner: After the patient was prepared and draped for operation, a plastic sheet was placed under the weighted retractor and draped over the lap of the operator. Every sponge was dropped into this lap sheet and periodically transferred to a basin containing sterile distilled water. At the completion of the operation the plastic sheet was wiped clean with a sponge moistened in the same water and then transferred to the basin. All of the sponges were then rinsed thoroughly in this water and the

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*Premarin, intravenous, was supplied by Ayerst Laboratories, New York, New York.

Table I. Average blood loss in vaginal hysterectomy with and without estrogen preoperatively

Procedure	Age 34-40		Age 41-46		Age 47-53		Age 54 and over	
	No.	c.c.	No.	c.c.	No.	c.c.	No.	c.c.
Vaginal hysterectomy without preoperative estrogen	32	278	21	239	12	203	6	139
Vaginal hysterectomy with preoperative estrogen	31	237	24	185	9	127	4	63
Decreased blood loss		41		54		76		76

Table II. Average blood loss in vaginal hysterectomy and repair with and without estrogen preoperatively

Procedure	Age 36-40		Age 41-46		Age 47-53		Age 54 and over	
	No.	c.c.	No.	c.c.	No.	c.c.	No.	c.c.
Vaginal hysterectomy and repair without preoperative estrogen	6	409	7	468	8	550	8	475
Vaginal hysterectomy and repair with preoperative estrogen	8	377	12	431	6	437	6	338
Decreased blood loss		32		37		113		137

entire solution sent to the laboratory for determination of the hemoglobin concentration of the solution.

The Coleman spectrophotometer was used to establish the hemoglobin concentration per 100 c.c. of blood before operation and the amount lost during the surgical procedure. The total blood loss was calculated from these 2 figures. Example: If the patient's hemoglobin was 12 Gm. per 100 c.c. before the operation and the hemoglobin recovered in the solution amounted to 58.1 Gm., the equation would be as follows:

$$12 - 100 :: 58.1 - X$$

The total blood loss would be 484 c.c.

Results

In the group of women upon whom vaginal hysterectomy was performed without preoperative estrogen, the average blood loss was greater in the younger than in the older age group. Thirty-two women between 34 and 40 years of age lost an average of 278 c.c. of blood, while 6 women in the postmenopausal age group lost only 139 c.c. In

patients who received preoperative estrogen, blood loss as compared with the untreated group decreased only slightly in each of the age groups. During the childbearing ages, 34 to 40 and 41 to 46, the decreases in blood loss were 41 and 54 c.c., respectively. In the menopausal and postmenopausal groups the differences observed in each were the same, 76 c.c. (Table I).

In the group of women upon whom vaginal hysterectomy with repair was performed, without preoperative estrogen, the average blood loss increased with age until the climacteric. Six patients between the ages of 36 and 40 years lost an average of 409 c.c. of blood, while 8 women in the postmenopausal group lost an average of 475 c.c. of blood. Women in the childbearing ages who were prepared with intravenous estrogen and upon whom the same procedure was performed lost an average of 32 c.c. less blood than those not estrogenically prepared. During the climacteric blood loss decreased 113 c.c. The decrease was 137 c.c. in the postmenopausal group (Table II).

Comment

Stammler and Warner reported an alteration in the clotting factor coincidentally with physiological changes in levels of estrogenic hormones during various phases of life.⁹ Estrogen excretion during childhood is minimal and equal in both sexes, rises sharply in the female shortly before the menarche and continues at different levels during the remaining years of life.

During pregnancy, when the estrogen secretion reaches a peak near term, there is an elevation in serum prothrombin conversion accelerator¹⁰ and fibrinogen¹¹ as well as a rise in the prothrombin level.¹² The same mechanism is observed in the newborn, estrogen secretion being high during the first few days of life.

In our study preoperative intravenous estrogen has no apparent effect on blood loss in women of the childbearing ages during either operative procedure. This may be explained by the normally high estrogen secre-

tion during this period of life. Reduction in blood loss, although slight, was seen in the menopausal and postmenopausal periods. The normally low estrogen level during this period of life may account for the benefit derived from the intravenous estrogen. Reports, to date, on decrease in blood loss following estrogen administration are devoid of statistical data, age, and sex of the patients studied.

Summary

A study was undertaken for the purpose of determining the effect of intravenous estrogen on blood loss during gynecological operations. One hundred women preoperatively received 20 mg. of intravenous estrogen, while 100 were used as controls. A slight decrease in blood loss following estrogenic preparation was noted, particularly in the menopausal and postmenopausal age periods during vaginal hysterectomy and vaginal hysterectomy with anterior and posterior repair.

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The value of intravenous pyelography prior to elective gynecologic operations

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IN THE course of preparing patients for elective pelvic operations and radiation therapy, it is customary to initiate various diagnostic and screening procedures. These are performed not only in an attempt to delineate and further define the gynecologic disease entity and insure the operative and postoperative welfare of the patient, but also to disclose unsuspected disease states which might compromise the patient's immediate and future well-being.

Generally accepted screening devices include general physical examination, complete blood count, serology studies, urinalysis, and chest roentgenograms. In addition, of course, diagnostic procedures dictated by specific symptomatology or physical findings are performed.

In addition to the above-enumerated screening procedures at the University of Missouri Medical Center, the Department of Gynecology has performed routine screening intravenous pyelographic studies on all patients admitted for elective major gynecologic operative procedures for a period of 2 years. Because it became apparent that a significant

number of unsuspected findings were evolving from the series, the question of including intravenous pyelography as a standard screening procedure prior to gynecologic operations was considered.

In an attempt to evaluate the advisability and potential effectiveness of making this procedure a routine one, this study was undertaken.

Procedure

Seven hundred and twenty consecutive gynecologic cases were evaluated for study purposes. In accordance with the usual pre-operative screening program, most of these patients underwent chest roentgenologic surveys. In addition, all who were to have major pelvic operations were subjected to routine intravenous pyelographic study.

Because of the established worth of chest roentgenologic screening, it was hoped that this investigation would reveal results elaborated by excretory urograms to be in some manner comparable to those elucidated by chest screening technique.

Results

Of the 720 gynecologic patients surveyed, 455 were studied by intravenous pyelography.

Significant, unsuspected pathologic conditions were found in 122 (26.8 per cent) of this group.

Several patients were found to have significant pathologic conditions of the genitouri-

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nary system as well as unsuspected extrarenal abnormalities.

One hundred (21.9 per cent) of the patients undergoing routine screening excretory pyelography studies showed significant unsuspected renal abnormalities while 29 (6.4 per cent) were demonstrated to have noteworthy extrarenal abnormalities.

Table I represents a breakdown of unsuspected pyelographic findings involving the renal excretory system.

Table II presents a similar breakdown of important extrarenal findings dependent on their demonstration to routine usage of screening pyelography.

In the total survey, 636 chest roentgenograms were taken. The total number of significant unsuspected findings was 29 (4.6 per cent). Table III demonstrates graphically an itemization of findings by chest film survey. Total effectiveness of the two screening procedures in terms of percentage yield of pertinent information is depicted in Fig. 1.

Comment

The relationship between the renal and reproductive systems in the female is a fundamental consideration essential to all endeavors in the field of gynecology.

From the standpoint of both clinical differential diagnosis and proposed operative technique, the renal excretory mechanism is of paramount importance to the physician treating diseases of the female pelvic genitals.

The genital and nephric systems are intimately associated in origin, development, and adult function. Both originating from the primitive genital ridge, these paired organ systems arise and function interdependently throughout fetal and adult life.

For these reasons, it is not surprising that disorders in one system are often reflected in secondary changes in the other. It has been well documented that diseases affecting the female pelvic genitals often affect and are reflected in anatomic deviations in the nephric system. Certainly this premise has been well exploited in the development of gynecologic diagnosis.⁹ The extension of cervical carcinoma into the parametrium and the de-

gree of potential ureteral occlusion engendered thereby is helpfully defined by renal contrast studies.³ Deviation in the ureteral course associated with large benign lesions of the uterus or adnexa, as well as congenital anomalies of the genital and renal tracts, may be ascertained in the same manner.¹

It is doubtful that any gynecologist fails to appreciate the benefits of renal radiographic studies, from a standpoint of both patient welfare and technical considerations.²

This investigative approach has been recommended as the best routine screening pro-

Table I. Unsuspected pyelographic findings involving the renal excretory system

Renal malignancy	1 (0.2%)
Genitourinary tract anomalies	24 (5.2%)
Chronic pyelonephritis	17 (3.7%)
Calculi, renal and ureteral	12 (2.6%)
Hydronephrosis and/or hydroureter	32 (7.0%)
Due to:	
Calculi	7
Malignant tumors	10
Benign tumors	15
Ureter deviated medially	14 (3.1%)

Table II. Extrarenal findings discovered by routine application of intravenous pyelography

Cholelithiasis	18
Internal biliary fistula	4
Metastases in ribs	2
Cystic lesions, femoral heads	3
Cholesterosis	1
Compression fracture L-2 and L-3	1
Total	29 (6.4%)

Table III. Unsuspected pathologic conditions revealed by routine chest film survey

Thyroid, substernal	3
Mediastinal mass	8
Tumor, lungs	3
Cervical ribs	2
Metastatic carcinoma, lungs	3
Heart disease, congenital	1
Bronchiectasis	3
Tuberculosis, active	1
Adenoma, thyroid	1
Tumor, cystic, rib	1
Compound fracture, dorsal rib	2
Aneurysm, thoracic	1
Total	29 (4.6%)

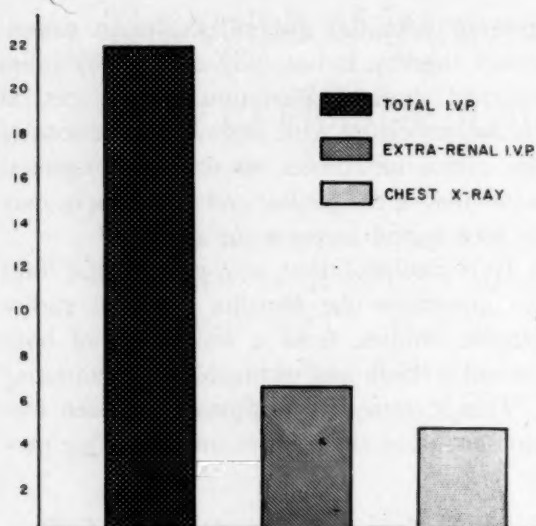


Fig. 1. Comparative effectiveness of routine intravenous pyelography and chest radiography in terms of percentage yield of information.

cedure for evaluating renal integrity in patients with cervical and prostatic malignancy. In addition, its use is recommended prior to and following operative procedures involving the renal excretory system.⁴

Although at present there are those advocating routine preoperative ureteral catheterization and others advising preoperative excretory pyelography,⁷ these procedures are not utilized uniformly by all gynecologists.

It was, therefore, of more than passing interest to us to note the incidence of highly significant unsuspected findings elaborated by a radiographic technique with established value in the field of gynecology, not widely incorporated as a routine preoperative screening measure.

From the statistics evolved in this study, it appears that routine pyelographic study prior to elective gynecologic operation is extremely productive of information important in the management of the gynecologic patient. This is true not only in terms of findings related intimately to the urinary system but also of extrarenal findings representing pathologic conditions of the same caliber as those demonstrated by chest radiologic techniques.

Although statistics from this survey would make it appear that routine pyelography in the patient being prepared for elective gynecologic operation is more than six times as

productive as chest screening, this is only as expected inasmuch as the screening target is intimately associated with the disease area. However, disregarding all pyelographic findings related to the renal system, it appears that excretory pyelography was productive of 6.3 per cent nonurinary tract new entities while routine chest films performed on the same group of patients revealed only 4.6 per cent hitherto undisclosed instances of pathologic findings.

Reactions to urographic contrast media are well documented and appreciated by those utilizing this technique.^{4-6, 8}

Pendergrass⁶ has collected perhaps the largest series of fatal reactions due to intravenous urography and has classified them as immediate and delayed, depending on the time of reaction in relation to time of administration of contrast media. Reactions reported with insufficient data were categorized as indeterminate. It would appear that the best prophylaxis available to the patient at the present time consists of careful attention to history of allergy and previous reactions to urographic study, intravenous testing with the contrast agent to be used, possible administrations of antihistaminics orally or intravenously prior to or with the injection of urographic media, and preparation for the administration of some type of emergency care.

Hamm⁴ recently reported a series of 21,525 intravenous urograms with 4 serious, nonfatal reactions. He stressed that this diagnostic test should not be used without indication.

In the series of intravenous pyelograms reported in this paper, no significant reactions were noted.

Summary

A high incidence of unsuspected pathology has been demonstrated by the routine use of intravenous pyelography in preparing patients for elective major gynecologic operations. In this series, in addition to disclosing a large number of unsuspected instances of genitourinary tract abnormalities, the screening technique was more productive in terms of disclosing unsuspected pathologic conditions,

exclusive of urinary tract abnormality, than the coincidentally performed chest radiographs.

It is not our purpose to detract from the importance of routine chest screening, to which the statistics included in this paper can only attest. It is our desire, however, to point out the advantages gained through routine intravenous pyelographic study to both the gynecologic patient and her physician.

Conclusions

1. Seven hundred and twenty gynecologic patients were surveyed; 455 of these patients underwent routine intravenous py-

elographic study in preparation for major pelvic operations; 636 patients received chest radiographs.

2. Unsuspected genitourinary tract pathologic conditions were disclosed in 26.8 per cent of patients by intravenous pyelography.

3. More unsuspected, incidental findings unrelated to the urinary tract were disclosed by excretory urography than by the coincidentally performed chest roentgenograms.

4. It is suggested that intravenous urography be included as a standard screening device for patients being prepared for elective major pelvic operations.

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Should hysterectomy replace routine tubal sterilization?

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STERILIZATION by surgical interruption of the continuity of the Fallopian tubes has become fairly commonplace. In most communities there now exists an appreciable number of women who have been subjected to this procedure. Consequently, it is not rare for a physician who deals with gynecological problems to see women with complaints related to the genital tract in whom previous tubal sterilization has been performed. What type of gynecological problems are encountered in such women? Does the procedure per se seem to enhance the possibility of subsequent gynecological abnormalities? Is there reason to believe that there is a deleterious "post-tubal sterilization syndrome"? This retrospective analysis was undertaken in an attempt to answer in some part these difficult and most perplexing questions.

Methods and material

A review of 670 tubal sterilizations done at Parkland Memorial Hospital from January, 1946, through December, 1956, was carried out. This period of time was chosen to supply a sufficiently large group of cases for critical analysis of subsequent gynecological difficulties. It was not continued

beyond December, 1956, so that a minimum of 2½ years and on the average 7 years has elapsed since the time tubal sterilization was performed.

The patients in this study were indigent or semi-indigent women who resided in the Dallas area. It is quite likely that in most instances where subsequent gynecological care would be sought, the patients would return to Parkland Memorial Hospital. This impression is supported by noting that 428 (64 per cent) have returned to this hospital as either outpatients or inpatients (but not necessarily with gynecological complaints) one or more times later than one year after tubal sterilization.

The diagnostic terms subsequently used are defined as follows: *Menorrhagia* was considered to be present if the patient complained of excessive bleeding during 3 or more cycles or if the observed bleeding resulted in the recommendation of uterine curettage. *Active pelvic inflammatory disease* was diagnosed only if acute salpingitis was seen at laparotomy or if tuboovarian or pelvic abscess was demonstrated. Otherwise patients with pelvic pain were classified as having pelvic pain of unknown etiology. *Great multiparity* refers to 8 or more pregnancies in which a viable fetus was delivered.

Results

Of the 670 tubal sterilizations reviewed, in 566 the Madlener technique and in 102 the Pomeroy procedure was carried out.

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The opinions expressed in this article are those of the author and do not necessarily represent the views or policies of the United States Air Force or the Department of Defense.

In 2 instances sterilization was accomplished by cornual resection. A total of 120 of the sterilizations were done at the time of cesarean section.

Age and parity. The average age was 31 years. The oldest patient was 48, and the youngest was an 11-year-old child with mitral stenosis and marked insufficiency who in 1954 had a therapeutic abortion with the sterilization. The average parity was 6 and ranged from zero to 15.

Indications. As shown in Table I, in 83.4 per cent of the 670 patients the indications were either great multiparity, hypertension, or repeat cesarean section. The category labeled "other" includes 13 separate diseases with no more than 3 cases under any one entity. In 15 of the 670 cases no specific indication was clearly stated.

Hospital stay and complications. The over-all postoperative hospital stay averaged 6.5 days with the shortest being 3

days and the longest being 43 days. This patient had tuberculous meningitis and died of the primary disease on the forty-third postoperative hospital day. The average postoperative hospital stay for those patients having only tubal sterilization as a surgical procedure was 5.2 days.

Complications arising from the operations (excluding those patients who also had cesarean section or vaginal plastic procedures) are listed in Table II. One of the patients developed a pelvic abscess and partial obstruction of the small bowel postoperatively. The abscess and bowel obstruction disappeared after antibiotic therapy. This was the only serious postoperative complication noted in this group.

Failures. A total of 22 failures (3.3 per cent) are known to have occurred to date. Out of 566 sterilizations by the Madlener technique there have been 21 failures (3.7 per cent) and of the 102 Pomeroy procedures there has been one failure (1.0 per cent). In the case of the failure with the Pomeroy technique one Fallopian tube and one fibromuscular structure, consistent with a segment of round ligament, was subsequently identified in the pathology laboratory.

Three failures (2.5 per cent) occurred following 120 sterilizations done at the time of cesarean section. All of these failures were in patients who had Madlener procedures. No failures occurred following the 27 tubal sterilizations in which there was no associated pregnancy.

In those patients with sterilization failure the average time from sterilization to conception was 16 months, ranging from 3 to 45 months. In all but one, conception occurred within 24 months.

Subsequent gynecological abnormalities. The subsequent gynecological abnormalities following tubal sterilization are listed in Table III. This demonstrates the over-all incidence of abnormalities as well as the incidence in the cesarean section and non-cesarean section groups. Of the 64 patients with menorrhagia, 2 had fibromyomas and 11 complained of stress incontinence. One

Table I. Indications for tubal sterilization

Indications	No.	%
Great multiparity	261	38.9
Hypertension	178	26.6
Previous cesarean section	120	17.9
Vaginal plastic operation	19	2.9
Chronic renal disease	17	2.2
Rheumatic heart disease	12	1.8
Tuberculosis	6	0.9
Diabetes	6	0.9
Rh incompatibility	5	0.8
Neuropsychiatric	5	0.8
Varices (extremities or vulvar)	5	0.8
Other	21	3.2
Reason not stated	15	2.3
Total	670	

Table II. Postoperative complications

Wound abscess	13
Adnexal hematoma	1
Pelvic abscess	1
Incisional hernia	7
Hematoma abdominal wall	2
Total	24
Per cent of 531 cases	4.5

Table III. Gynecological abnormalities (exclusive of pelvic pain) after tubal sterilization

	<i>Cesarean section group</i>	<i>Non-cesarean section group</i>	<i>Total</i>
Total No. of sterilizations	120	550	670
Menorrhagia	9 (7.5%)	55 (10.0%)	64 (9.50%)
Active pelvic inflammatory disease	2 (1.7%)	5 (0.92%)	7 (1.40%)
Fibromyomas	1 (0.8%)	4 (0.73%)	5 (0.71%)
Carcinoma cervix (noninvasive)	0 (0.0%)	3 (0.55%)	3 (0.45%)
Carcinoma cervix (invasive)	1 (0.8%)	0 (0.00%)	1 (0.02%)
Carcinoma uterus	0 (0.0%)	1 (0.02%)	1 (0.02%)
Total No. of abnormalities	13	68	81 (12.10%)

of the post-cesarean section patients with menorrhagia had stress incontinence. Twenty-two (12.3 per cent) of the 178 patients with hypertension had menorrhagia in subsequent years.

Subsequent gynecological operations. Sixty-eight patients (10 per cent) have subsequently had gynecological operations. These are listed in Table IV. In 2 of the patients in which the Marshall-Marchetti operation was carried out, previous anterior colporrhaphy had failed. Of the 13 patients who had subsequent vaginal hysterectomy for menorrhagia, the indications for operation in 7 also included stress incontinence and relaxation of the pelvic floor.

Comment

That tubal sterilization is a surgical procedure that can be performed with safety is well borne out by these results. One death from tuberculous meningitis followed tubal sterilization. No deaths attributable to the operation occurred. The reported mortality has ranged from zero to 0.7 per cent,¹⁻⁷ excluding Lazard's personal series with 2 deaths in 27 cases.⁸

The 4.5 per cent incidence of postoperative complications found in these patients is low. The one major complication in the 531 patients who had tubal sterilization as the only surgical procedure was a pelvic abscess and partial small bowel obstruction which were treated successfully with antibiotics and gastrointestinal suction.

It is well established that failure of tubal

sterilization does occur. Garb in a recent review reports the incidence of failure in the reliable literature to be 1.44 per cent with the Madlener technique and 0.4 per cent with the Pomeroy method.⁹ Dieckmann and Jensen believed the major cause of failure to be surgical ineptness.^{4, 7} The 3.3 per cent incidence of failure at Parkland Memorial Hospital during a 13 year period is considerably higher than that reported by Garb, and probably not infrequently did result from surgical ineptness. Most of these failures occurred during a 5 year period in which the procedure was performed by rotating interns, through a minute incision, and under local anesthesia. It was also under these circumstances that the single failure with the Pomeroy method occurred. Here a portion of round ligament instead of Fallopian tube was resected.

A failure rate of 2.5 per cent in those instances where the procedure was performed at the time of cesarean section is similar to the reports of others.⁸⁻¹⁰ The lower failure rate in patients sterilized at the time of cesarean section supports the views of Dieckmann and Jensen in that cesarean sections were performed by obstetrical residents rather than rotating interns.

Menorrhagia was the most common single complaint of the patients after sterilization. The incidence of at least 9.5 per cent falls between that found by Prystowsky (4.6 per cent), and that found by Williams (16.5 per cent) and Jensen (25 per cent).^{3, 7, 11}

It is difficult, if not impossible, to estimate how many of these women would have had excessive bleeding if the sterilization had not been performed. Williams and co-workers,¹¹ analyzing the histories obtained from 3,222 women during pregnancy, noted that 5.1 per cent of them described abnormally heavy menstrual bleeding sometime prior to the onset of pregnancy. Greene has estimated that at least 10 per cent of women during the period from menarche to menopause will at some time complain of menorrhagia.¹² The data obtained from this study do not substantiate the impression of some that tubal sterilization considerably enhances the likelihood of abnormal bleeding. Furthermore, it should be noted that while at least 9.5 per cent of these patients have been subsequently diagnosed as having menorrhagia, less than 3 per cent have had menorrhagia of sufficient intensity to result in its treatment by hysterectomy.

Williams, in his series, found that one third of the patients with hypertension subsequently developed menorrhagia, and he stated that the subsequent bleeding problems in this group were related to the hypertension rather than to any direct effect

of the tubal sterilization. Hennessy has stated that hypertension per se causes menorrhagia.¹³ In the Parkland Memorial Hospital group of 178 patients with hypertension only 12.3 per cent had subsequent menorrhagia. This is only slightly higher than the 9.5 per cent frequency of menorrhagia in the over-all group, and it fails to support Williams' view.

Pelvic inflammatory disease was proved in one per cent of the patients subsequent to the sterilization procedure. This is certainly a much lower incidence than in the general female population seen at Parkland Memorial Hospital. Likewise, in only 0.75 per cent of patients have significant fibromyomas been found.

Two of the noninvasive carcinomas of the cervix were found 9 years after tubal sterilization. One of the noninvasive carcinomas of the cervix was detected 8 months after tubal sterilization, and the invasive carcinoma of the cervix was diagnosed 18 months after tubal sterilization. These latter two lesions probably could have been found prior to tubal sterilization if routine prenatal cytological and histological examination of the cervix had been done. How many

Table IV. Subsequent gynecological operations

	Cesarean section group (120)	Non-cesarean section group (550)	Total
Hysterectomy for:			
Menorrhagia	1	17	18 (2.70%)
Stress incontinence	1	9	10 (1.50%)
Fibromyomas	0	3	3 (0.45%)
Carcinoma cervix (noninvasive)	0	3	3 (0.45%)
Unknown	0	1	1 (0.15%)
Cesarean hysterectomy	2	3	5 (0.75%)
Cesarean section and repeat tubal sterilization	1	0	1 (0.15%)
Repeat tubal sterilization	0	4	4 (0.60%)
Marshall-Marchetti procedure	0	3	3 (0.45%)
Perineal plastic operation	0	3	3 (0.45%)
Salpingo-oophorectomy	1	2	3 (0.45%)
Dilatation and curettage for:			
Radium implant (carcinoma)	1	1	2 (0.30%)
Menorrhagia	2	7	9 (1.35%)
Retained secundines	0	1	1 (0.15%)
Cervical polyp	0	1	1 (0.15%)
Exploratory laparotomy for:			
Acute salpingitis	1	0	1 (0.15%)
Total	10	58	68
Percentage incidence	8.3	10.5	10.20%

of the remainder of these patients will subsequently develop cervical carcinoma is a matter of conjecture. Adequate cytological and histological study of the cervix during pregnancy should aid materially in reducing the number to a minimum.

Pelvic pain for which the etiology was unknown has been the complaint of 4.3 per cent of these women at some time following tubal sterilization. Physical findings revealed, at most, adnexal tenderness. It seems unlikely that the sterilization operation in this small group of patients directly caused or contributed significantly to this pain. Furthermore, it is most unlikely that simple hysterectomy would have been followed by a lower frequency of this complaint.

The incidence of 10 per cent subsequent gynecological operations is almost identical to the 9.29 per cent reported by Prystowsky.³ There is no appreciable difference between the cesarean section and non-cesarean section groups.

In the past 20 years several articles have been written advocating the widespread use of hysterectomy or cesarean-hysterectomy for sterilization.^{1, 8, 11, 14-21} The rationale in these articles has usually been the prevention of subsequent gynecological disease and further surgical procedures, as well as the production of absolute sterility. Dyer condemns the practice of elective cesarean-hysterectomy simply for sterilization but states that in cases where at the time of cesarean section there is uterine pathology or the uterus has reached a "saturation point from repeated cesarean sections," cesarean-hysterectomy is often indicated.²²

Tubal sterilization is a surgically safe and, under optimal conditions, effective method of preventing future pregnancy. More extensive operations involve a greater cost not only in monetary terms but also in terms of morbidity and probably mortality. The results of this survey suggest that the routine use of hysterectomy for purposes of sterilization is not warranted. It is more logical to remove the uterus only in those relatively infrequent cases where hysterectomy is indicated because of disease of the

uterus or failure of its supporting structures. Otherwise, early puerperal tubal sterilization is the procedure of choice. This survey further reveals that tubal sterilization is entitled to more dignity as a surgical operation than it has sometimes received in the past and that it should be performed by someone properly trained to do so with all of the safeguards utilized in performing other operations.

Summary and conclusions

A review of 670 tubal sterilizations at Parkland Memorial Hospital from 1946 through 1956 was accomplished; 566 were Madlener procedures, 102 were Pomeroy procedures, and 2 were cornual resections. In 83.4 per cent of cases the indications were either great multiparity, hypertension, repeat cesarean section, or some combination of these three.

The over-all failure rate was 3.3 per cent with 3.7 per cent in the Madlener group and 1.0 per cent in the Pomeroy group. The majority of failures were thought to result from surgical ineptness.

No deaths occurred which were attributable to the operation. The only serious complication was a pelvic abscess with partial small bowel obstruction which was treated satisfactorily with antibiotics.

The most frequent postoperative gynecological complaint was menorrhagia, known to have occurred in 9.5 per cent. The incidence of subsequent operation for gynecological diseases has been 10 per cent.

Tubal sterilization does not seem to contribute significantly to gynecological dysfunction other than to render the patient sterile. Tubal sterilization is a relatively safe and adequate procedure in adept hands, and the routine use of hysterectomy simply to accomplish sterilization is unwarranted.

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The obstetric sequelae of major operations on the uterine cervix

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MUCH has been done and is still being done to remedy the lot of the childless couple. Similarly, advances in obstetric training, practice, and facilities have relegated much of the disaster of former years to the archives. Against these considerations, changing trends in the diagnosis and prevention of genital malignancy combined with a widening of the indications for plastic vaginal operation have gradually introduced, to our everyday practice, new problems in the salvage of pregnancy and the anticipation and treatment of a type of dystocia hitherto infrequently encountered.

I decided to investigate, in retrospective fashion, the aftermath, in terms of productivity, of operations involving disturbances of the normal cervical anatomy. In a brief review of authoritative sources, there would appear to be general agreement concerning the adverse effects upon subsequent pregnancy which follow amputation of the cervix.^{2, 13, 15} Zoefgen in 1936, quoted by Te-Linde,¹⁵ even advised high cervical amputation as a definitive sterilization procedure. As will be seen, this latter concept is certainly untenable as it stands; but in general I have been able to confirm the widely held view that such operations lower the conception rate and increase the tendency to abortion, especially in the second trimester, but they less markedly increased the hazards of subsequent labors as far as the present series showed.

From the South Belfast Group of Hospitals.

The material studied in the first instance consisted of a group of 122 women under the age of 40 who were submitted to cervical amputation usually as a component of the Fothergill colporrhaphy. These patients were operated on by a total of 6 surgeons at the Samaritan Hospital for Women, Belfast, between 1951 and 1956. The patients prior to operation were all parous women of average fertility. None were advised specifically to avoid pregnancy after the operation. All were told of the prognosis for any future pregnancy in comparatively favorable terms although hospital delivery was recommended. In each case, very definite symptomatology was present before operation, and the procedure was deferred in those women actually planning a further pregnancy until this hope was achieved or abandoned because of the severity of the condition and intolerance of conservative therapy.

The results of the investigation, obtained by written questionnaire, are reproduced in Tables I to III. I did not feel justified in recalling the patients for follow-up examination, as considerable distances were involved and it was thought that little actual benefit could be offered to the patients in return for the journey, especially as it was presumed that most would be satisfied with the operations or they would have reported or been referred earlier. As will be observed, a significant number of these patients actively avoided pregnancy, either from fear of causing recurrence of the prolapse or because their families were considered complete. Though not concerned with the pres-

ent communication, it is noteworthy that voluntary complaints of dyspareunia after vaginal plastic operations were obtained in a considerable portion of cases. The foregoing, perhaps coupled with physiologic waning of fertility with age and unrecorded emotional and family difficulties, may weight the figures in an unduly adverse fashion.

To compare these figures with those reported elsewhere, a further table was constructed which tends, in as far as the results can be analyzed, to bear out the trend displayed in the present survey (Table IV).

A further investigation was made by examining the obstetric history, after cervical amputation of a group of 19 consecutive grand multiparas who were delivered at the Royal Maternity Hospital, Belfast, between the years 1951 and 1956. This latter smaller series (Table V) is, in my view, a less biased one in that these patients were for the most part taken from groups in which emotional factors played little part in their marital lives and who were largely precluded from taking active contraceptive precautions.

Comment

From any angle, the gynecologist must accept a responsibility for some lowering of absolute fertility potential and increase of the hazards of labor when he removes part or all of the uterine cervix in women of childbearing age. An effort has been made to assess the extent of the physician's part in so limiting a woman's family. It will be agreed that there is a definite ground for considering carefully the obstetric future before embarking on any such procedure.

Against this conservative attitude, the modern indications for tissue removal on or about the cervix must be closely examined. No woman should, in my opinion, be condemned for any prolonged period to the wearing of a pessary for genital prolapse or relaxation. The so-called pessary life is, in the best of circumstances, a mere existence possibly with long-term risk. These views are substantiated by Averill,¹ Hunter,⁶ and Malpas.¹⁰ Attention, though, is directed to the findings of Finn³ and Hoag and Hill,⁵

who found close approximation in their respective clinics between the general abortion rate and that following cervical amputation. These authors have perhaps added a more encouraging note to the opinions hitherto advanced. It must be remembered, however, that general abortion rates cannot be reasonably compared with those in women positively known to desire children unless the criminal factor is excluded. This latter is almost impossible to assess accurately and varies with race and community.

The trend is to attempt to prevent subsequent malignant change in the cervix by vigorous therapy in those cases best described by the late Sir Charles Read¹² as the "dirty cervix." I hold strong views on the importance of generous cone biopsy and electrocoagulation in such cases. This is particularly indicated in areas such as Northern Ireland where cytologic study is not generally

Table I. Amputations of cervix

Ward patients circularized	98
Replies received	62
Known to have left the country	6
Unaccounted for	30
Amputation combined with plastic repair	95
Amputation alone	3

Table II. Gross results from 62 cases*

Became pregnant	9 (12 pregnancies, 1 unplanned)
Contraception	38
Failed to conceive	15 (3 sterilized at operation, 1 hysterectomy a year after operation)
Total	62

*Two patients required repeat repair, 1 after term delivery; 8 patients complained of severe dyspareunia. Corrected number definitely exposed to pregnancy, 21.

Table III. Fate of pregnancies achieved*

Abortion before 14 weeks' gestation	3
Abortion after 14 weeks' gestation	1
Premature labor	2 (36 weeks, 29 weeks)
Term deliveries	6 (1 patient twice)

*Nine out of 21 patients exposed to pregnancy conceived (42 per cent); 5 out of 12 pregnancies ended before 30 weeks (one living infant) (41.6 per cent).

Table IV. Pregnancy outcome following cervical amputation

	Cases	Total pregnancies	Abortions	Premature labor
Present series (1959)	62	12	4	2
Solomons ¹⁴	62	25	11	Not stated
Hunter ⁶ (collected)	92	132	13	19
Williams (quoted by Hunter ⁶)	37	49	20	8
Shaw ¹⁵	2,000	27	Not stated	Not stated
	(all ages)			

Table V. Nineteen consecutive cases of delivery

Abortions before 14 weeks' gestation	3
Abortions after 14 weeks' gestation	0
Premature labor	2
Delivery after 37 weeks' gestation	30
Fetal loss (neonatal death unconnected with operation)	1
Obstetric abnormalities	6
Delay in labor, secondary cervical dystocia	2
Complete tear	2
Cervicovaginal tears	2

available. On these grounds, a certain proportion of patients will be exposed to the risks previously outlined, yet, this must be regarded as a small price to pay to secure relative immunity from neoplasia.

Why do these patients lose their pregnancies prematurely and why do a proportion of those who carry to term experience obstetric difficulty? Most are agreed that cervical incompetence accounts for the first group, especially when the vaginal cervix has been amputated to any extent, although Miller and Todd¹¹ found that 18 per cent of women becoming pregnant after conization had premature labor. Secondary cervical dystocia, especially in Jeffcoate's^{7, 8} opinion, after conization and diathermy, accounts for the majority of delayed labors noted after operation on the cervix. It must not be forgotten that scarring and reduced distensibility of the tissues following operation lay the patient open to risks of severe intrapartum trauma.

Finally, it seems opportune to mention certain techniques and prophylactic measures which may lessen the aftereffects while not narrowing the scope of cervical operation

which, it has been pointed out, is increasingly indicated and has too often in the past been denied. First, amputations of the cervix should be limited in extent or dispensed with, if possible, in operations for prolapse in younger women.^{1, 10} Possible alternatives are simple parametrial advancement,¹⁴ the cuff operation⁶ and vaginal ventrosuspension via the anterior cul-de-sac (which Hunter attributed to the late Louis B. Phaneuf and to Cullen).

Patients who have had abortions after cervical amputation and perhaps some of those who have not should be prophylactically dealt with by some modification of the Shirodkar procedure such as the occlusive trachelorrhaphy described by Hall.⁴ With a similar object in view, I place 2 sutures of the type described by Lash and Lash⁹ at the level of the internal os when performing cervical amputation in younger women.

The management of labor in such cases is beyond the scope of this paper, but vigilance of a high order with a liberal attitude towards cesarean section is required. In Britain, elective section is not frequently performed in these cases except following successful cure of stress incontinence; but ruptures of the vault and lower segment are frequently reported, with occasional fatalities, which tend to broaden one's mind toward abdominal delivery.

Summary

1. The recognized sequelae of major operations on the uterine cervix are considered.

2. A study of the obstetric careers of two groups of women after such procedures is presented.

3. The foregoing results are compared with those of other workers.

4. The modern indications for amputation or conization of the cervix are briefly considered.

5. Methods of management designed to forestall the previously considered sequelae are briefly described.

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Culdoscopy in gynecologic diagnosis

A review of 404 cases of endoscopic examination

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CULDOSCOPY has a special place among gynecologic diagnostic procedures. Certain pathologic conditions in the pelvis remain in the sphere of conjecture despite the numerous laboratory aids at our disposal and the ease with which the genital organs may be palpated. Furthermore, gynecologic conditions are frequently diagnosed incorrectly as psychosomatic illnesses because the pelvic examination fails to reveal any abnormality.

Many an unnecessary explorative laparotomy may be prevented by culdoscopy and, on the other hand, findings on culdoscopy may present an absolute indication for laparotomy in instances in which operation was not previously considered. A particularly outstanding feature of culdoscopy is the role it can play in the examination and evaluation of the Fallopian tubes in cases of sterility. Endocrinologic problems may also be solved at times after direct visual examination of the ovaries. As a result of experience gained over the past 3 years our¹ approach to several clinical problems has changed from basically one of palpation to one of direct visualization of the pelvic organs by means of the culdoscope.

Methods

A Gulbring culdoscope with a visual angle of 45 degrees and a field of vision of 60 degrees was used. Ancillary instruments in-

cluded a standard gas apparatus for performing pneumoperitoneum, trocars, and equipment for salpingography.

The lithotomy position described by Palmer² was preferred to the knee-chest position of Decker.³ The patient is placed on the table in the dorsal position, legs suspended half-bent, and buttocks overlapping the edge. She is fixed in this position by shoulder supports. A vaginal speculum is introduced and the posterior lip of the cervix fixed by Pozzi forceps. The vagina is painted with iodine; the table is tilted in Trendelenburg position, at approximately 30 degrees, to allow the intestinal loops to gravitate upward. The exact spot where the vaginal wall is fixed to the cervix is located by testing with pickup forceps; the puncture should be made 15 mm. posterior to this point in the midline.

With the cervix fixed in position by the Pozzi forceps, the trocar with its cannula is plunged as far as the metal collar in the direction of the center of the pelvis. The trocar is then withdrawn, and the tube of the insufflator is fixed to the cannula. Carbon dioxide is then introduced. It should flow in painlessly without any rise of pressure. The injection of about 2 L. is sufficient.

The insufflation cannula is withdrawn and introduced into the uterus, which can now be tilted to an anteverted position and maintained at this angle. The endoscope is immediately introduced through the trocar opening in the posterior portion of the vagina and passed into the center of the pelvis and, later, directed toward the umbilicus.

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At the termination of the culdoscopy, pressure is applied to the abdomen to enable the maximum amount of gas to escape, and the table returned to a horizontal position. Antiseptic gauze is inserted into the fornix and the speculum withdrawn. The patient is not permitted to sit up for 3 hours.

We carry out the majority of our culdoscopies under thiopental sodium anesthesia preceded by morphine and atropine. The advantages are: (1) the patient is easy to position and the desired position is maintained without difficulty; (2) the Fallopian tube can be studied from end to end with greater ease because it more often "hangs" unrolled along the length of the ovary, instead of being prolapsed in the ovarian fossa as in Decker's technique.

We feel that the lithotomy position is more physiologic, more comfortable for the patient, and more practical for the physician.

Most of the patients were discharged on the day following the examination. Fifteen remained an extra day because of severe pain in the shoulder region, and a few remained 3 days after the examination because of low-grade fever.

Material

Over 400 culdoscopic examinations have been performed in our department. Previous to culdoscopy, the patients have been divided into 6 main groups according to the clinical diagnosis based on case history, clinical signs and symptoms, findings on physical examination, and various laboratory tests (Table I).

Results

Sterility. One hundred and eighty-four patients with sterility were chosen for further investigation by culdoscopy, after routine examinations had failed to reveal the exact lesion. This group of sterile women were subdivided as follows: (1) 148 who had occluded tubes as shown by salpingography and tubal insufflation; (2) 15 in whom no anatomic or functional abnormality could be found; and (3) 21 who were suspected of having genital tuberculosis. In these cases

culdoscopy was performed before tubal insufflation or salpingography because of the danger of re-exacerbation of the inflammatory process.

In the patient with occluded tubes who was being considered for plastic operation, the decision as to the feasibility of operation and the prospects for success are best determined by visual examination. The above-mentioned patients underwent culdoscopy with this object in view.

Culdoscopic findings sometimes contradict the results of insufflation and salpingography. A positive Rubin test may be obtained when, on culdoscopic examination, the tubes are seen to be long, tortuous, infantile, and with poor physiologic function. On the other hand, we have seen cases in which insufflation and repeated x-ray examination showed blocked tubes, whereas, under endoscopic visualization the tubes were seen to be normal and patent. These cases stress the importance of tubal spasm in negative insufflation tests and hysterosalpingograms.

Tuberculosis of the tube appears in four different forms: miliary, nodular, adhesive, and ordinary salpingitis. In the miliary form, a growth of characteristically whitish granulations is noted on a tube of more or less normal dimensions though often adherent. The miliary growths may be limited to the tube or may extend to the uterus and the tubes, or may form a part of the miliary tuberculosis of the peritoneum. In the nodular form the tube shows yellowish serosal protuberances throughout the length and at the end. In the adhesive form the adnexa are entirely submerged by edematous and congested adhesions, but diagnosis is often possible from the presence of some miliary granulations.

The effect of modern antimicrobial therapy on tuberculosis of the genital organs can be visually assessed by the culdoscope.

Endocrine disturbances. Routine clinical examination often fails to reveal pathologic changes in the ovaries, such as hypoplasia, agenesis, or the presence of a polycystic condition.

The findings on culdoscopy in 15 cases of

Table I. Division of cases according to tentative diagnosis

<i>Tentative diagnosis</i>	<i>No. of cases</i>
Sterility	184
Menstrual and endocrine disorders	50
Prolonged abdominal pain	63
Suspected ectopic pregnancy	45
Suspected tumors of pelvic organs	26
Nongynecologic disease	16
Inability to carry out satisfactory vaginal examination	20
Total	404

Table II. Findings on culdoscopic examination in 184 cases of sterility

<i>Reason and findings</i>	<i>No. of cases</i>
Tentative diagnosis of occluded Fallopian tubes	148
Hydrosalpinx	57
Tubal occlusion in isthmal portion	48
Adhesions and sacculations	26
Patency of tubes (indigo carmine)	17
No pathologic abnormalities found in the preliminary routine examinations	15
Confirmation of normal condition	13
Tuberculosis of the genital organs	2
Tuberculosis suspected in the genital organs	21
Normal condition	17
Genital tuberculosis	4

Table III. Diagnosis of amenorrhea at culdoscopic examination

<i>Diagnosis and findings</i>	<i>No. of cases</i>
<i>Primary amenorrhea</i>	
Male pseudohermaphroditism	1
Polycystic ovaries (Stein-Leventhal syndrome)	4
Turner's syndrome	2
No pathologic findings	8
Total	15
<i>Secondary amenorrhea</i>	
Polycystic ovaries (Stein-Leventhal syndrome)	10
Cystic ovaries	7
Hypoplastic ovaries	2
No pathologic findings	16
Total	35

primary amenorrhea and 35 cases of secondary amenorrhea are summarized in Table III.

Difficulties are frequently encountered in palpating polycystic ovaries, particularly when the patient is obese, as she so often is when the Stein-Leventhal syndrome is present.

Recurrent lower abdominal pain of undetermined cause. A large percentage of patients visiting gynecologic outpatient clinics complain of recurrent lower abdominal pain. In many there is little correlation between the complaint and the pelvic findings on bimanual examination. Many such women are labeled neurotic or psychotic, while others go from one physician to the next seeking and receiving palliative treatment that has no relation to the basic cause of the pain. These pains, appearing before or at menstruation, may be the result of organic changes which can be revealed only on direct visual inspection.

We studied the cases of 60 patients referred to our department for lower abdominal pain. All had complained for at least 6 months, and all had undergone unsuccessful therapy. The results of culdoscopic examinations are given in Table IV.

Physical examination does not always reveal endometriosis, adhesions, or a chronic inflammatory process. Then, too, attacks of lower abdominal pain accompanied by slight peritoneal irritation may present a very difficult diagnostic problem.

In the course of our study, several cases of intraperitoneal bleeding were encountered. The differential diagnosis between ectopic pregnancy, ruptured cyst, endometriosis, and retrograde menstrual bleeding could be made only with the aid of the culdoscope.

Three cases in which peritoneal irritation and severe abdominal pain occurred during the first few days of menstruation were proved by culdoscopy to be retrograde menstrual bleeding and not dysmenorrhea. The intrapelvic menstrual blood was responsible for the clinical picture of peritoneal irritation.

In 2 of these cases, the cervix was blocked by submucous myomas, while the third patient was admitted with a typical history for an ectopic pregnancy. Culdoscopy refuted this diagnosis by showing that the peritoneal reaction was due to menstrual blood in the abdominal cavity.

Endoscopic visual examination thus revealed the true diagnosis of a clinical condition without specific physical findings. The clinical picture gave the impression of an ectopic pregnancy: severe lower abdominal pain, peritoneal irritation, and tenderness in the pouch of Douglas.

It appears that retrograde menstrual bleeding is less rare than was previously thought when the only means of diagnosis was by direct visualization. This diagnosis must be borne in mind in certain clinical states, especially after induced abortion and other trauma in the region of the cervix.

The whole question of retrograde menstrual bleeding has been dealt with elsewhere.

Ectopic pregnancy. The diagnosis of ectopic pregnancy cannot always be made with certainty by routine physical examination, urine tests for pregnancy, and puncture of the pouch of Douglas.

Forty-five patients underwent all of the routine examinations as well as puncture of the pouch of Douglas and curettage because of suspected ectopic pregnancies. In none could the diagnosis be positively proved or ruled out.

Of the total of 45 cases of clinically suspected ectopic pregnancies, 14 were confirmed. Normal pelvic organs were seen in 9, while in the remaining 22 tumors, endometriosis, or inflammatory changes were found (Table V).

We have relied on pelvic puncture and the appearance of free or coagulated blood to confirm the suspicion of ectopic pregnancy. In our opinion, and in that of many others, this is a most reliable test. It is, however, not infallible. Two cases of bleeding from a wound in the posterior wall of the uterus, one of hematoma of the ovary, and one of puncture of the broad ligament are

examples confirmed by culdoscopy in which puncture of the pouch of Douglas gave false positive results.

Special diagnostic problems arise where two pathologic conditions are present. This is especially true when a tumor of nontubal origin tends to disprove the presence of an ectopic pregnancy.

Tumors of the pelvic organs. The nature and origin of tumors of the pelvic organs sometimes present a formidable diagnostic challenge. Not every tumor requires surgi-

Table IV. Findings in cases of recurrent lower abdominal pain at culdoscopic examination

<i>Findings</i>	<i>No. of cases</i>
Reflux of menstrual blood into the peritoneal cavity	5
Endometriosis	4
Multiple adhesions with congestion	10
Prolapse of polycystic ovary into the pouch of Douglas	4
Chronic adnexitis	6
No pathologic findings	33

Table V. Findings on culdoscopic examination in 31 cases in which ectopic pregnancy was not confirmed

<i>Diagnosis</i>	<i>No. of cases</i>
Simple ovarian cyst	12
Corpus luteum cyst	5
Ovarian endometriosis	1
Acute adnexitis	4
No pathologic findings	9

cal removal. An exact diagnosis may, therefore, prevent unnecessary laparotomy while, on the other hand, surgical interference may be indicated.

Of a group of 26 patients who had been referred to our department for surgical intervention because of pelvic tumors, approximately 60 per cent were found not to require operation after culdoscopic examination. In the remaining 10 patients, operation confirmed culdoscopic findings in regard to origin and localization of the tumors.

Complications and failures

No serious problems in connection with this examination have been reported in the literature when only appropriate cases are selected and every complication is diagnosed early.

The only major complication is injury to the rectum. Abarbanel⁴ reported 5 cases of damage to the rectum found in 400 patients who had undergone culdoscopy. Jasey⁵ reported 2 such injuries in 594 examinations. Subperitoneal emphysema, especially associated with Decker's method, was the second most prominent complication noted in the literature; Fortier⁶ reported 5 typical cases.

The endoscopic examination could not be completed in 20 of our 404 patients. In one case, we were forced to interrupt the examination because of an anesthetic complication. In 7, we were unable to penetrate the pouch of Douglas. In another 10 patients, the genital organs could not be visualized because of multiple adhesions. There were 2 cases of retroperitoneal perforation of the rectum; both patients had uneventful recoveries, each requiring three additional days of hospitalization.

One patient required suturing because of vaginal bleeding. In one, a piece of omentum prolapsed through the wound in the pouch of Douglas; it was sutured and excised.

Comment

Much experience had to be gained before we were able to evaluate the true size of the organs, since evaluation depends upon the distance of the organ from the lens. Some of our early complications must be accounted for by the team's lack of experience in the methods and technique of this procedure.

Culdoscopy is of great value in the examination of the pelvic organs. Only by this method can the differential diagnosis between a pedunculated subserous myoma and a solid ovarian tumor be established with finality, despite the ease of manual palpation of the uterus. Hypoplasia of the uterus, congenital deformities, endometriosis, and local

adhesions can be readily observed by culdoscopic examination. It is our opinion that the main value of culdoscopy is in the examination of the ovaries and the Fallopian tubes. Kelly⁷ found pelvic conditions which would interfere with reproduction in 222, or 53.2 per cent, of 417 patients on whom he successfully performed culdoscopic examinations. Changes in the ovaries which cannot be evaluated by any other method may be seen.

Insufflation and salpingography alone cannot supply all of the information required regarding the Fallopian tubes in cases of sterility. These routine examinations show only the state of the lumen, and do not reveal peritubular adhesions, tortuosity, adhesions of the fimbriae, endometriosis, or tuberculosis. We have described elsewhere⁸ a number of diagnostic mistakes made on the basis of tubal insufflation and salpingography which were found only on culdoscopy.

Summary

The results of 404 consecutive cases of culdoscopic examination are presented.

The value of this diagnostic procedure is paramount in cases of sterility and some endocrine disturbances.

Investigation of lower abdominal pain of unknown origin by means of this examination revealed several examples of retrograde tubal menstruation. This occurrence is not as rare as was previously believed.

Culdoscopy is safe with minimal complications when sufficient experience has been gained.

The examination speeds up diagnosis and shortens hospitalization.

Culdoscopy reduces diagnostic errors to a minimum.

In some instances, visualization of the pelvic organs prevents unnecessary exploratory laparotomies and gives positive indications for surgical treatment.

No tubal plastic operation should be undertaken before a culdoscopy has been performed.

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New inflatable uterotubal cannula for gas insufflation

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MANY cannulas for use in uterotubal insufflation have been described. Since the diameters and shapes of cervixes vary considerably, the use of a metal- or solid rubber-tipped cannula presents problems in sealing the juncture of the tip and the cervix. Leakage at this juncture interferes with proper pressurizing of the uterotubal channel. Also leakage at this juncture may create sounds which may mimic the sounds produced by gas escaping from the fimbriated ends of the tubes if auscultation is used for confirmation of patency.

If too much pressure is used to approximate the solid tip to the cervix in order to avoid this leakage, it frequently becomes painful to the patient. Also great pressure from a hard tip often traumatizes the cervix.

Hollow rubber balloons can be inflated to seal off body orifices with much more comfort to the patient and with much less danger of trauma. Balloon-tipped catheters for trachea and urethra are well-known examples.

The cannula* (Fig. 1) described herein embodies a rubber balloon at its tip and has been used successfully in gas insufflation of the uterotubal channel. It is not suitable for liquid injections.

This cannula has the following advantages over other cannulas previously described:

1. The balloon conforms easily, quickly, and comfortably to almost every shape of cervix.

2. The balloon-loaded cannula can be boiled in water or pressure sterilized.

3. The cannula is less likely to get plugged up on account of its double lumen and, if thorough cleaning is desired, the balloon can be removed and replaced quickly and easily by an attendant (Fig. 2).

4. It can also be replaced by a nurse or operator with a new balloon if the rubber is torn or deteriorates from use, or if a new balloon is desired.

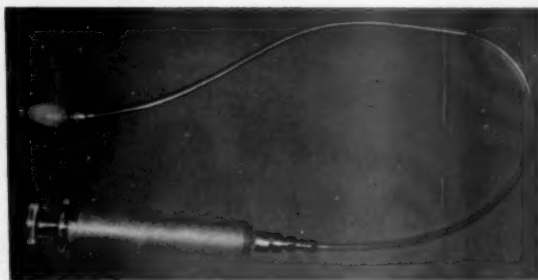


Fig. 1.

5. The metal tube through the center of the fusiform balloon is made of more flexible metal for easy bending to facilitate passage through an angulated cervix.

6. The proximal metal handle is made of stiffer metal which while it allows bending will not bend too easily on handling.

Directions for use

At the first insufflation a preliminary sedative may be desirable as the uterine cavity should be first entered with a uterine sound to determine if the cervicouterine channel is patent and if any angulation is present.

*Milex Products, 5915 Northwest Highway, Chicago 31, Illinois.

Since a uterine sound measures 10 Fr. and the tip of this cannula measures 11 Fr., further dilation in addition to the uterine sound is seldom necessary. A tenaculum, gently applied, may be necessary to straighten out any marked angulation but, after the first insufflation, a tenaculum is seldom necessary.

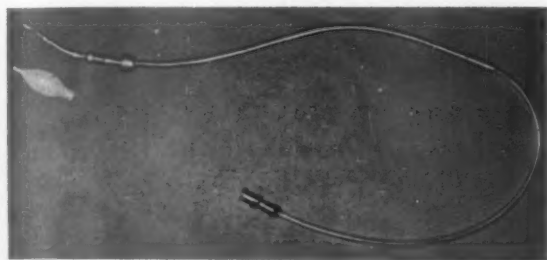


Fig. 2.

With the adapter at the end of the plastic tube connected to a syringe or other reservoir, and manometer or kymograph, the tip of the cannula is passed into the cervical

canal until the rear metal sleeve is pressed against the external os. With the cannula held in place with one hand, gas is injected from the syringe or other reservoir in the usual manner. The gas pressure also will inflate the balloon and thus prevent any leakage. Releasing the pressure will deflate the balloon and the cannula can be removed easily.

To replace the rubber balloon, the small and large metal nuts are unscrewed and the old balloon removed. The metal tip of the cannula is wetted with water or glycerine. The tip is slipped into the balloon, passing through the larger end of the balloon first. The metal nuts are screwed back on, capping the rubber ends of the balloon. The cannula now may be sterilized in antiseptic, boiling water, or pressure sterilizer. Or the metal cannula and the balloon may be sterilized separately and assembled together under sterile conditions.

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An inexpensive apparatus for tubal transufflation with carbon dioxide

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TUBAL transufflation with air involves the risk of gas embolism and death. This danger is much less with carbon dioxide, because it is highly soluble in plasma.

One is tempted to use air because the necessary equipment can be improvised easily from sphygmomanometer parts, while apparatus for carbon dioxide insufflation costs at least \$100 (not including the manometer).

Why is equipment for tubal transufflation using carbon dioxide so expensive? Carbon dioxide is readily available only as a highly compressed gas. To use it safely in tubal transufflation one must reduce its pressure, and all commercially available equipment does this by fairly complicated means.

The apparatus described here provides carbon dioxide under low pressure. Any physician can assemble it from a sphygmomanometer and a few parts he can buy for less than \$15. It permits the insufflation of carbon dioxide in controlled amounts and under exactly measured pressure.

It uses a *toy balloon* as low-pressure gas reservoir. Should one accidentally leave the high-pressure tank valve open, the balloon would burst at a pressure much lower than even the usual insufflation pressure. The transufflation pressure is produced by a sphygmomanometer bulb, and while one could create a dangerously high intrauterine gas pressure by pressing the bulb too often and too hard, this practically will not happen, as one watches the manometer while pressing the bulb and one always feels the pressure produced.

An emergency tire inflator and fire extinguisher for automobiles, sold by automobile accessory stores and dry ice and carbon dioxide dealers, is the source of the gas. It costs, filled, about \$5.00, and contains enough carbon dioxide for hundreds of tubal transufflations. A large toy balloon is attached to it; one cuts a hole into its closed end, slips it over the tank outlet and fastens it with tape. The open end of the balloon is attached to the sphygmomanometer bulb. Either a bulb with the air intake at the "South Pole" (the pole opposite the flow-regulating valve), or one open at the valve end only may be used. If a bulb with the intake at the "South Pole" is used, the open end of the balloon is slipped over the bulb and fastened with tape (Fig. 1). If a closed-end bulb with an Air-Flo* valve is used, a cut-off injection needle is soldered into the air intake hole of the valve and the toy balloon (or tubing coming from the balloon) is attached to the needle hub. The sphygmomanometer valve is connected by plastic tubing to the sphygmomanometer (mercury or aneroid) and to the cervical cannula. (Plastic infusion tubing, such as Cly-Q-Pak†, catalogue No. 4434, serves well and costs little.)

Part of this equipment cannot be sterilized. A glass adapter filled with absorbent cotton and sterilized by autoclaving, placed between the cannula and the tubing, would provide adequate filtration of bacteria and

*W. A. Baum & Co., Inc.

†Abbott Laboratories.

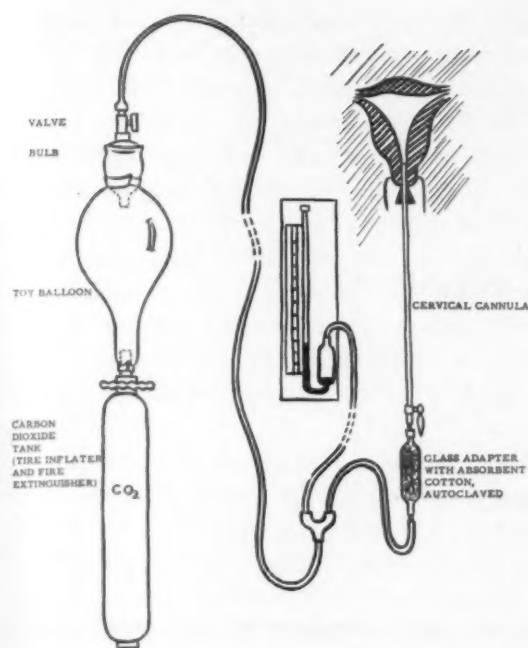


Fig. 1. Diagram of tubal transufflation apparatus. For details see text. This diagram shows a bulb with gas intake at the "South Pole."

practical sterilization of the gas.¹ I have, however, used this equipment many times without such a sterile filter and I have never seen an infection following its use.

Procedure for use

Partially distend the balloon with carbon dioxide. Attach one free end of the tubing to the manometer. Squeeze the bulb a few times to remove the air from the tubing. Attach the other free end of the tubing to the cannula in the uterine cervix. Slowly squeeze the bulb while you watch the manometer. Judge tubal patency by the behavior of the built-up gas pressure, by abdominal auscultation, or by both. One compression of the bulb expels about 25 cubic cm. of gas. After the test, question the patient for shoulder pain.

Any physician can assemble this apparatus from equipment he owns and from a few parts (tire inflater, toy balloon, cervical cannula, and infusion tubing) which he can buy at little expense. Thus, there is no reason to use air in tubal transufflation.

My thanks are due Mrs. J. C. Kuppinger, Harlingen, Texas, for making the drawing reproduced in Fig. 1.

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OBSTETRICS

Placenta and myometrial block

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THE discovery of progesterone stimulated extensive research in biology and obstetrics. The results obtained could be best explained by assigning a key role to this steroid in the maintenance of pregnancy.^{4, 16}

Reviews of the more recent literature note,^{7, 8} however, that striking species differences were reported in the effects of ovariectomy, oxytocin, and progesterone treatment upon the maintenance and termination of pregnancy. These species differences were regarded by some investigators^{3, 15} as evidence that the basic mechanism by which pregnancy is maintained and terminated is different in women from that in laboratory animals.

This significant conclusion is by no means conclusively supported. Controversies with respect to the general significance of progesterone in regulating the pregnant uterus could be reduced or eliminated by considering the inadequacy of different techniques used in studying uterine motility; by determining hormone concentrations in target structures, for example, in cell membranes rather than in body fluids; and by a

better understanding of the progesterone effect itself.

This paper reports new information concerning the nature of the progesterone effect. The observation⁵⁻⁷ that progesterone blocks the propagated activity of the myometrium and that the placenta exerts a local influence on the site of its attachment is confirmed and extended. The local blocking effect imposed upon the placental bed by a functional placenta is significant in that it provides a mechanism by which the maintenance and termination of pregnancy can be explained in women as well as in laboratory animals, in spite of seemingly discrepant findings.

The present experiments were stimulated by the theory^{7, 8} that placental attachment, which determines the success of pregnancy, must be secured in spite of the "hostile" environment of a contractile bag, the uterus. This attachment, mechanically speaking, cannot be very firm, as evidenced by ready detachment at the end of normal labor, yet during delivery of the fetus it must be maintained at all costs in a strongly contracting uterus. That the fetus does not play a decisive role in safeguarding placental attachment through a "splint-like" action on the uterine bag is demonstrated by the fact that the removal of the fetus does not lead to placental detachment.¹⁷ The observation¹² that the attachment of the placenta is in-

From the Rockefeller Institute.

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fluenced by the endocrine state of the animal prompted the challenging supposition that the placenta acquires endocrine functions in order to influence directly the contractility of the placental bed and thereby control placental attachment. A local effect on the placental bed would permit safe attachment, on the one hand, and adequate mechanical activity for delivery in the rest of the uterine wall, on the other. It is this local blocking effect of the placenta which we now demonstrate experimentally.

Background information for the study of the propagated activity of the uterus. When all cells of a uterine strip are stimulated simultaneously in a longitudinal electric field (60 cycles per second, 1.5-2.0 volts per centimeter, 5 seconds' duration), activity is uniform along the length of the muscle in both the estrogen- and progesterone-dominated uterus. The tension so induced cannot be increased by moderate depolarization, or by substituting chloride in the Krebs solution with members of the halogen series, or by pharmacological stimulation. Since all cells are simultaneously and maximally activated, the mechanical response of the uterus is not dependent on the ability of its excitable membrane to propagate the wave of electrical excitation. However, activity does depend on other properties of the membrane, e.g., when the membrane potential is drastically reduced by excess potassium or by calcium deficiency the optimum tetanic stimulus no longer excites.^{5, 7, 8}

The intact estrogen-dominated uterus, however, need not be stimulated simultaneously at all points. Maximum tension can be triggered by stimulating one end of the muscle only, for activity is readily propagated to the unstimulated portions. The progesterone-dominated uterus, on the other hand, is activated only at portions where directly stimulated. If the stimulus is applied at one end of the muscle, only the stimulated portion responds mechanically, as indicated by tension measurements. Such a uterus is nonpropagating^{5, 7, 8} because of the blocking effect of progesterone.

Tension recording, however, describes propagated and nonpropagated activity only qualitatively. Propagated activity at different portions along the length of the uterus is more accurately measured by the fluorescent dye method of Mashima and Csapo.¹⁴ This technique photographically records differential shortening, during the entire contraction cycle, along the length of the muscle performing isotonic work.

Methods

We used New Zealand white rabbits at different stages of pregnancy. The duration of gestation was determined by observing the moment of successful mating. We adapted the technique, designed for experiments on cross-striated muscle, by preliminary tests on strips from 3 nonpregnant rabbits. After the technique had been worked out we studied propagation in uterine strips from four early pregnant animals; eleven 24-30 days pregnant; three 30-day-pregnant rabbits after placental dislocation; four parturient animals; and four postpartum animals. Observations were usually made on more than one strip from the same uterus.

Uterine strips about 8 cm. long and about 0.3 to 0.5 cm. wide were removed from the anesthetized animal, and mounted in a 10 by 10 cm. square Lucite chamber 2 cm. deep. The chamber was filled with mammalian Krebs solution, oxygenated with 95 per cent oxygen and 5 per cent carbon dioxide, and at a constant temperature of 37° C. The uterine strip was marked off into 4 segments by spotting on its surface a nontoxic fluorescent dye (RCA material No. 33-Z-607). The afterloaded (5 g) muscle was then stimulated and the movement of the illuminated marks was photographed on tri-X film by a constant speed motion picture camera (Dumont, type 321-A).

The strip was either stimulated at all points simultaneously or else at one end only. For the former stimulus we applied longitudinal electric fields set up between two platinum plate electrodes covering the opposite sides of the chambers. Stimulation in the latter case was done by 2 ring-shaped

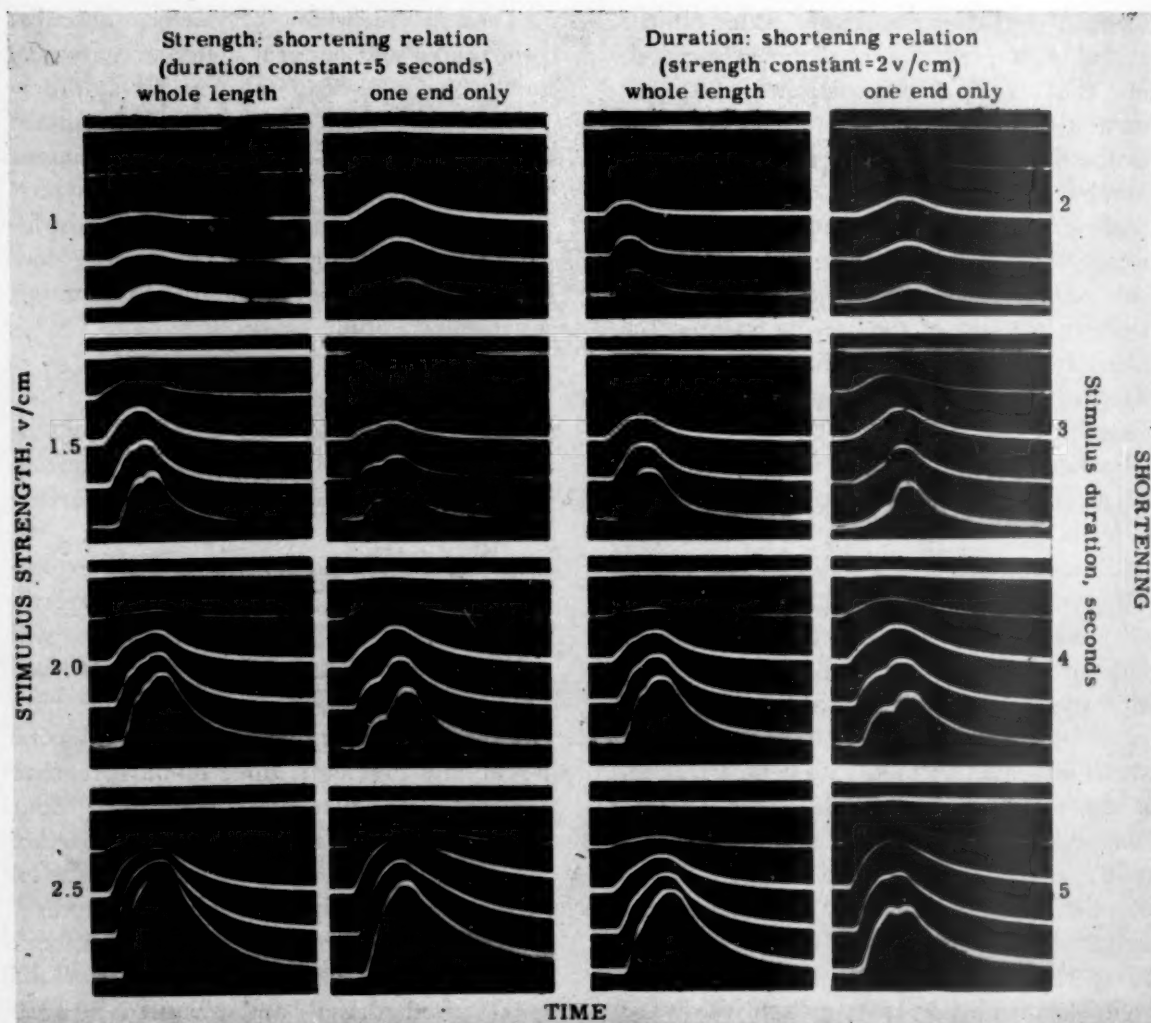


Fig. 1. Rabbit uterus, 1 hour post partum.

platinum wire electrodes placed at one end of the strip. In the first case the muscle was independent of its ability to propagate the wave of activity, in the second it was dependent on propagation. The field strength in both cases was 2 volts per centimeter, 60 cycles per second, alternating current, 5 seconds' duration. The films obtained were projected and enlarged, enabling us to measure differential shortening along the length of the uterine strip by comparing the length of each segment at rest with that at the peak of maximum activity.

Results

Our findings may be best demonstrated by the original records illustrating characteristic

uterine behavior at different stages of pregnancy. The postpartum (estrogen-dominated) and early pregnant (progesterone-dominated) uteri are similar in that excitability in both preparations is uniform along the length of the uterine horn. But whereas the former one is propagating the latter is nonpropagating. Functional placentas upset this uniformity of uterine excitability and the late pregnant and parturient uteri consist of distinctly propagating (interplacental) and nonpropagating (placental) portions. This functional inhomogeneity disappears after the delivery of the placenta or can be experimentally suspended by dislocating the placenta more than 24 hours before observation.

Fig. 1 illustrates the relationship between the strength (left) and duration (right) of stimulation and shortening. The strip is taken 1 hour after spontaneous delivery of both: fetuses and placentas. The uterine strip is stimulated (using different field strengths and durations) either throughout its entire length or at one end only. At threshold strength and duration both types of stimuli are rather ineffective. But when the stimulus becomes optimal, the uterine strip shortens along its whole length irrespective of whether the whole length or only one end of the

muscle is stimulated. This is evidence of propagation.

Fig. 2 illustrates the characteristically different property of the early pregnant (progesterone-dominated) uterus. The animal is 3 days pregnant. Progesterone is produced by the corpora lutea of the ovaries and the progesterone effect is uniform along the length of the uterine horn, presumably because the hormone is uniformly distributed by the blood stream. When such a uterus is stimulated simultaneously at all points along its length at different field strengths (left)

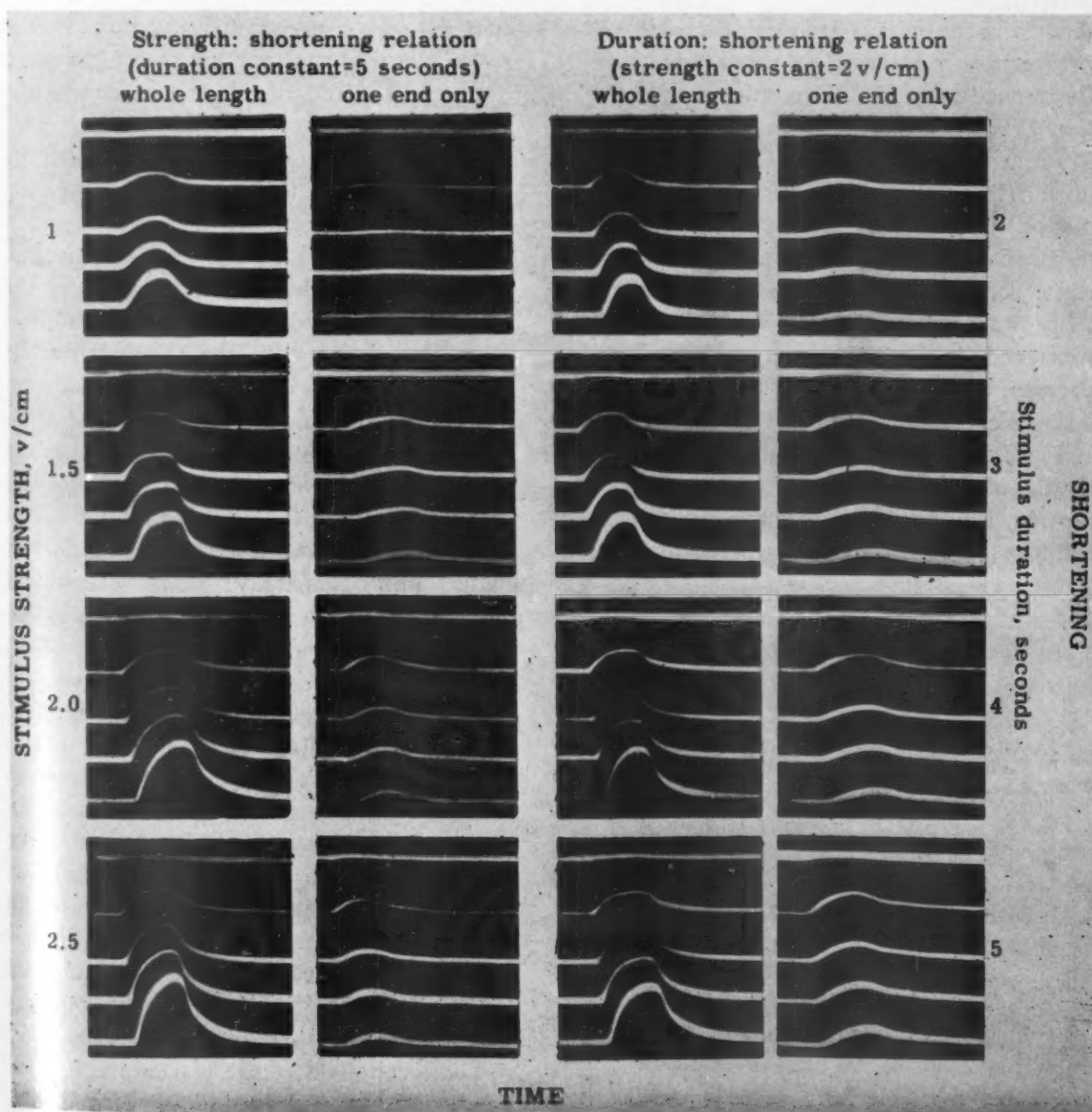


Fig. 2. Rabbit uterus, 3 days pregnant.

and durations (right), activity is uniform along the length of the strip. But when only one end of the preparation is stimulated, activity is limited to the stimulated portion and does not spread to the unstimulated portion. This is evidence of the blocking effect of progesterone.

While the postpartum uterus is uniformly propagating and the early pregnant uterus is uniformly nonpropagating, the late pregnant uterus consists of segments which are propagating and others which are nonpropagating. Fig. 3 illustrates the local influence of the placenta on the propagated activity of the uterus. The animal is 25 days pregnant. This particular rabbit was pregnant in one horn only and was therefore specifically suited for the demonstration of the placental effect on conduction. When a uterine strip from the nonpregnant horn (first row) was stimulated at all points simultaneously (2 volts per centimeter, 5 seconds' duration) all portions became activated. When only one end of the strip was stimulated all portions again shortened, but activity was moderate, and decreased with the distance from the stimulating electrodes.

The strip from the pregnant horn (consisting of a placental and a nonplacental portion, Fig. 3, second and third rows) also exhibited uniform activity when stimulated

simultaneously at all points along its length (left). When its placental end was stimulated, however, the activity remained localized in the portion between the electrodes (second row, right). When, on the other hand, the nonplacental end was stimulated, activity did spread with some delay to the adjacent region and only ceased at the nonplacental-placental junction (third row, right). This is evidence of the local effect of the placenta on the propagated activity of the uterus.

The fact that a difference in the propagating activity was observed not only between the placental and interplacental portions of the pregnant horn, but also between the placental portion of the pregnant horn and the nonpregnant horn, makes the demonstration the more striking.

In a series of experiments illustrated by Fig. 4 we sought to learn how long during gestation the placental bed of the uterus is influenced by the local effect of the placenta. We have raised this question in view of the fact that about 50 per cent of our rabbits went into delivery on the thirtieth day of gestation when labor was induced by oxytocin.⁵

The experimental strips consisted of a placental and a nonplacental portion. The uterine strip from the normal rabbit, 30 days pregnant (left row), was activated maximally and uniformly when stimulated simultaneously at all points (first). When only its nonplacental end was stimulated, activity spread to the adjacent portion and thus all the nonplacental half of the strip became active (second). Activity, however, stopped at the nonplacental-placental junction. When, on the other hand, the placental end was stimulated, only the segment between the electrodes became active and the adjacent half of the placental portion remained inactive (third). This is evidence of the local effect of the placenta on the placental bed of the 30 days pregnant uterus.

The local effect of the placenta is further documented by withdrawal symptoms. If the placenta is detached mechanically 24 hours

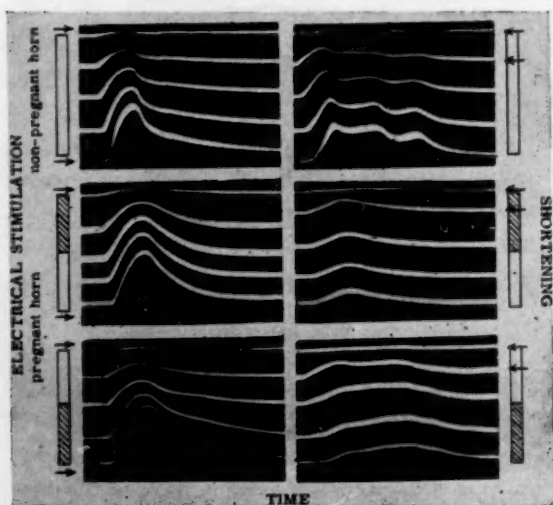


Fig. 3. Rabbit uterus, 25 days pregnant.

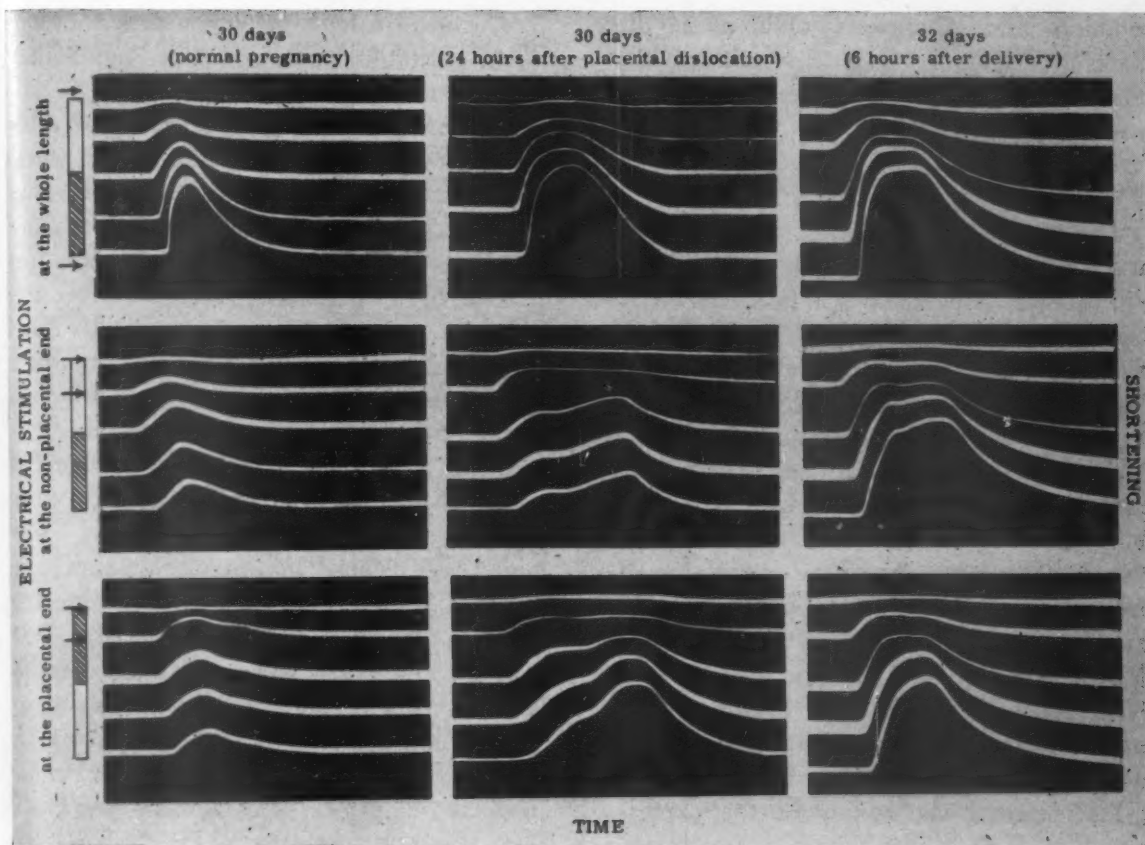


Fig. 4. Rabbit uterus, pregnant.

prior to such an experiment as just described, a characteristic change is observed in the propagated activity of the uterus (middle row). As before, the uterine strip is uniformly and maximally activated when the stimulus is applied simultaneously at all points (first). However, the duration of the contraction cycle is notably prolonged. When the nonplacental end is stimulated, only the nonplacental half becomes active and the activity does not spread to the placental portion (second). This is evidence that 24 hours after the dislocation of the placenta the uterus did not completely recover (on the thirtieth day of pregnancy) from the local placental effect. That this local effect is partly withdrawn is demonstrated by the next experiment (third). When the placental end is stimulated, activity does spread over to the adjacent placental portion, and, of course, once the placental half of the strip is activated, activity does spread over to the nonplacental portion. The end result is that

the whole strip is uniformly activated. What we see here is an intermediate condition between block and well-propagated activity.

The placental effect is normally withdrawn when the placenta is expelled after spontaneous delivery (right row). In a uterine strip removed 6 hours post partum, consisting as before of a placental and a nonplacental portion, the local effect of the placenta can no longer be demonstrated with the present technique. The strip is activated at all points irrespective of how the stimulus is applied, namely at all points simultaneously (first) or only at the non-placental end (second), or only at the placental end (third). The postpartum uterus is propagating at all points along its length.

These experiments on the propagated activity of the uterus in late pregnancy clearly demonstrate that a pregnant uterine horn is functionally inhomogeneous. The inhomogeneity is associated with placental

function and disappears only after the placenta is spontaneously delivered, or if the placental function is suspended experimentally.

Comment

The results presented may be better appreciated if one recalls that the only physiological substance which has been shown to exert a blocking action on the propagated activity of the uterus is progesterone⁵ and that this same steroid can prolong pregnancy beyond term in physiological quantities.^{4, 5, 16} A number of considerations suggest that the relation between muscle block and maintenance of pregnancy is causal rather than coincidental. First of all, the suspension of function in excitable tissues is generally accomplished by blocks. Second, the withdrawal of the block and the onset of delivery follow a similar time course. Third, progesterone treatment at term sustains the muscle block and pregnancy as well.

The internal consistency of the experiments performed in rabbits is reassuring. What is being challenged, however, is their general validity and their applicability to women. Until recently it was generally believed that pregnancy cannot be predictably induced in women by oxytocin until term approaches. The clinical experience suggested that in women as well as in rabbits the progesterone block must be withdrawn before the uterus responds to pharmacological stimulation. This is a reasonable assumption in spite of the fact that effective progesterone treatment could not be demonstrated in late pregnancy,⁹ but only in early pregnancy.¹ It had been suggested^{7, 8} that the progesterone doses are still inadequate, or that the systemically applied progesterone does not reach the target cells in sufficient quantity. Indeed, intra-amniotic administration was shown to be very effective in rabbits,¹³ and encouraging results were also reported in women.¹¹ Furthermore, recent experiments¹⁸ with radioactive progesterone suggest the progesterone output in women is more (300 to 600 mg. per day) than previously assumed and used therapeutically.

The observation^{2, 3, 15} which does not seem to fit with this picture is that "labor-like" intra-amniotic pressure changes can be induced in the human uterus already at mid-pregnancy by high oxytocin infusion rates. This finding was interpreted as meaning that uterine activity in women does not depend, as in rabbits, on the controlling influence of progesterone, but rather on the oxytocin concentration of the blood. This conclusion meets with difficulties because the observation itself cannot be readily interpreted in terms of progress in delivery. It has the advantage of being performed in women. But intra-amniotic pressure does not describe uterine contractility unequivocally. The formula, intra-amniotic pressure times frequency equals uterine activity, is subject to criticism in that pressure in a closed system (like the uterus) is not a straight function of the active area. Pascal's law states in fact that the pressure is independent of the area under compression. Thus, when oxytocin increases intra-amniotic pressure to a "labor-like" quantity in a midpregnant uterus, one does not learn whether a small or a large fraction of the uterine wall is activated. Progress in labor, on the other hand, would seem to depend on the area activated, and it is interesting to note that women in midpregnancy do not easily go into labor, even if they eventually do so after several days of treatment with massive doses of oxytocin.

Thus, many of the observed facts can be reconciled if we assume that the human uterus, endocrinologically and functionally, is an inhomogeneous or asymmetrical organ. The asymmetry would result from the progesterone effect of the placenta, more marked at the placental bed of the uterine wall than at other portions. That the rabbit uterus in late pregnancy is not a uniform muscular tissue is demonstrated by the inhomogeneity of the membrane potential at different uterine portions,¹⁰ by experimental asymmetrical deliveries,¹³ and specifically by the present experiments. These observations would seem to make clinical studies very feasible, experiments which would determine

whether the human uterus is a homogeneous or an asymmetrical contractile bag. The outcome of such experiments would greatly facilitate the interpretation of existing data and could much improve our understanding of parturition and the management of pregnancy and delivery. It could explain the ancient puzzle: how does the uterus deliver selectively its two passengers (fetus and placenta) at different times, or how is placental attachment maintained in the "hostile" environment of a strongly contractile, parturient uterus?

Summary

The fluorescent dye method of Mashima and Csapo was employed in a study of the propagated activity of the pregnant rabbit uterus.

Mechanical activity induced by stimulating one end of an 8 cm. long uterine strip was well conducted along the entire length of the *postpartum uterine strip*. This is evidence of propagation. The extent of activity was dependent on the strength and duration of electrical stimulation, as characteristic of excitable tissues.

The uterus in early pregnancy (before implantation) showed activity strictly restricted to the stimulated portion, due to a uniform block exerted on the entire length of the uterine horn. In the *late pregnant uterus* the block was no longer uniform but it was restricted to the placental portion of the uterine wall. The interplacental regions and the nonpregnant horn of the pregnant uterus did propagate the wave of activity to some extent. This segmental distribution of propagating and nonpropagating regions, in the pregnant uterus, results in functional inhomogeneity.

Functional inhomogeneity is characteristic of the rabbit uterus in late pregnancy; the pregnant horn becomes fully propagating and of uniform activity after the placenta is born, or if placental function is suspended before term.

Addendum. While this article was in print two papers have been published, both supporting our demonstrations of the local effect of the placenta on the myometrium.^{19, 20}

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Effect of conduction and inhalation anesthesia on uterine contractions

Experimental study of the influence of anesthesia on intra-amniotic pressures

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DIAMETRICALLY opposed statements regarding the effects of spinal anesthesia on uterine contractions appear in the literature.¹⁻³ These stimulated us to study amniotic pressures and uterine contractility, before and after the use of various types and levels of spinal anesthesia, and various kinds and degrees of inhalation anesthesia.

Information concerned with uterine contractility in humans has been gathered by clinical observations, by biostatistical evaluations of the duration of labor, by the use of the external tokodynamometer,^{4, 5} and by measurements of electric potentials.⁶⁻⁸ A more exact method had not been available until Alvarez and Caldeyro-Barcia⁹ in South America, and Hendricks¹⁰ in this country, introduced the technique of studying uterine contractility by continual recordings of the intra-amniotic pressures. Our previous experience¹¹ with this method assured us of its accuracy and safety.

Materials and method

Sixty normal pregnant patients at term or in labor were selected for this study. The

uterine contractions before and after the administration of the anesthetic were measured by continuous recording of the amniotic fluid pressures. A thin polyethylene catheter was introduced through the anterior abdominal wall into the amniotic cavity and connected to a pressure transducer and direct-writing oscillograph.

The intensity of each myometrial contraction was recorded as the increase in amniotic fluid pressure (mm. Hg) caused by the contraction. The frequency of contractions was expressed as the number of contractions per 10 minute period. The basal uterine tonus in each individual experiment was indicated by the pressure exerted by the myometrium (about 10 mm. Hg) upon the amniotic fluid between contractions.

By definition,¹² the tonus of smooth muscle is its resistance to stretch. This resistance or response to stretch in the myometrium varies with uterine contraction and with other conditions which affect the state of uterine smooth muscle. Since the contents of the uterus are partly but not completely compressible, normal uterine contractions are both heterotonic and heterometric. The pressure between uterine contractions represents the intrinsic contractile response of smooth muscle to the changing volume of the uterine contents, i.e., the tonus of uterine smooth muscle under these conditions.

The intraperitoneal pressure was measured

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as the pressure within the urinary bladder which contained no more than 20 c.c. of urine. The base line of the intra-amniotic pressure was set at the highest level of the intraperitoneal pressure. The height of one small square on the oscillogram represents a pressure of 10 mm. Hg. The breadth of the same square represents a time interval of 20 seconds. The curve representing a change in the intra-amniotic pressure as a result of a uterine contraction during labor is characteristic (Fig. 1, *A* and *B*). It rises steeply from the resting pressure, reaches a rounded peak, and gradually returns to the precontraction level. Any extrinsic pressure, be it external, from palpation, or internal, from coughing or straining, appears as irregular breaks in the normal smooth curve of uterine contraction (Fig. 1, *C*). Therefore, records of curves with these irregularities were not considered in the analysis.

During labor the intrauterine pressures in the absence of straining are commonly 55 to 60 mm. Hg, but, as Reynolds¹³ has observed, after dilatation of the cervix and during expulsion of the head in the same patient, the intrauterine pressures in the absence of straining may be only 50 mm. Hg. When expressed as an index of contractility ($C_i = P \times F$, C_i = index of contractility, P = pressure, F = frequency), this decrease in intrauterine pressure with a fully dilated cervix would represent only 15 to 20 C_i units (Montevideo units according to Caldeyro-Barcia), but the decrease could falsely be attributed to the effect of anesthesia when the evaluation is made in absolute figures. This must be borne in mind in interpreting the effect of anesthesia on uterine contractions, and the data described in this paper take this point into account.

Results

In view of the many factors affecting uterine contractility, only patients without obstetric complications were selected for the continuous recording of the intra-amniotic pressures. One exception was made, namely, the inclusion of a patient who had an anencephalic fetus and polyhydramnios.

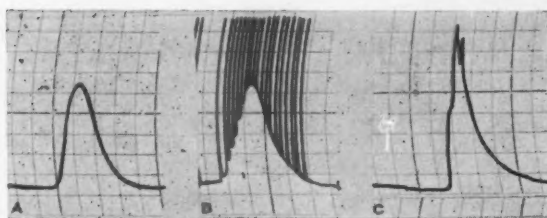


Fig. 1. *A*, A typical curve of uterine contraction. *B*, A typical curve of uterine contraction. Vertical lines represent flushing of the tube. *C*, An atypical curve. "Bearing down" pressure is superimposed upon a uterine contraction.

Spinal anesthesia. Twenty-three patients in various stages of labor (designated in each record by the degree of cervical dilatation and the level of the vertex in relation to the pelvic planes) were given a spinal anesthetic while the intra-amniotic pressures were recorded. Sensory levels of anesthesia as high as T-2 and C-6 were reached in 6 patients; in 14 patients the sensory levels were estimated to be between T-10 and T-5. In the remaining 3, the levels were below T-10.

Sensory anesthesia, T-2 to C-6. It is evident from the records that levels of sensory anesthesia as high as T-2, T-1, and C-6 did not affect the frequency, intensity, or tonus of the uterine contractions (Fig. 2, *A*, *B*, and *C*). The intensity, tonus, and frequency of uterine contractions, however, changed in one of these patients when marked hypotension resulting from the high spinal anesthesia developed, and in another patient when marked hypertension was induced by intravenous methoxamine (Vasoxyl) following a short hypotensive episode.

Fig. 3 shows the course of the uterine contractions before and after spinal anesthesia with the sensory level to T-2 and circulatory depression with a moderate degree of shock. The uterine contractions prior to the anesthetic were 35 to 40 mm. Hg in intensity and irregular in frequency and intensity, although a pattern of "bigemini" contractions is apparent. The intrauterine pressure between contractions was 5 to 10 mm. Hg and steady. Following the injection of the spinal anesthetic, the patient's blood pressure dropped in 5 minutes from 120/80

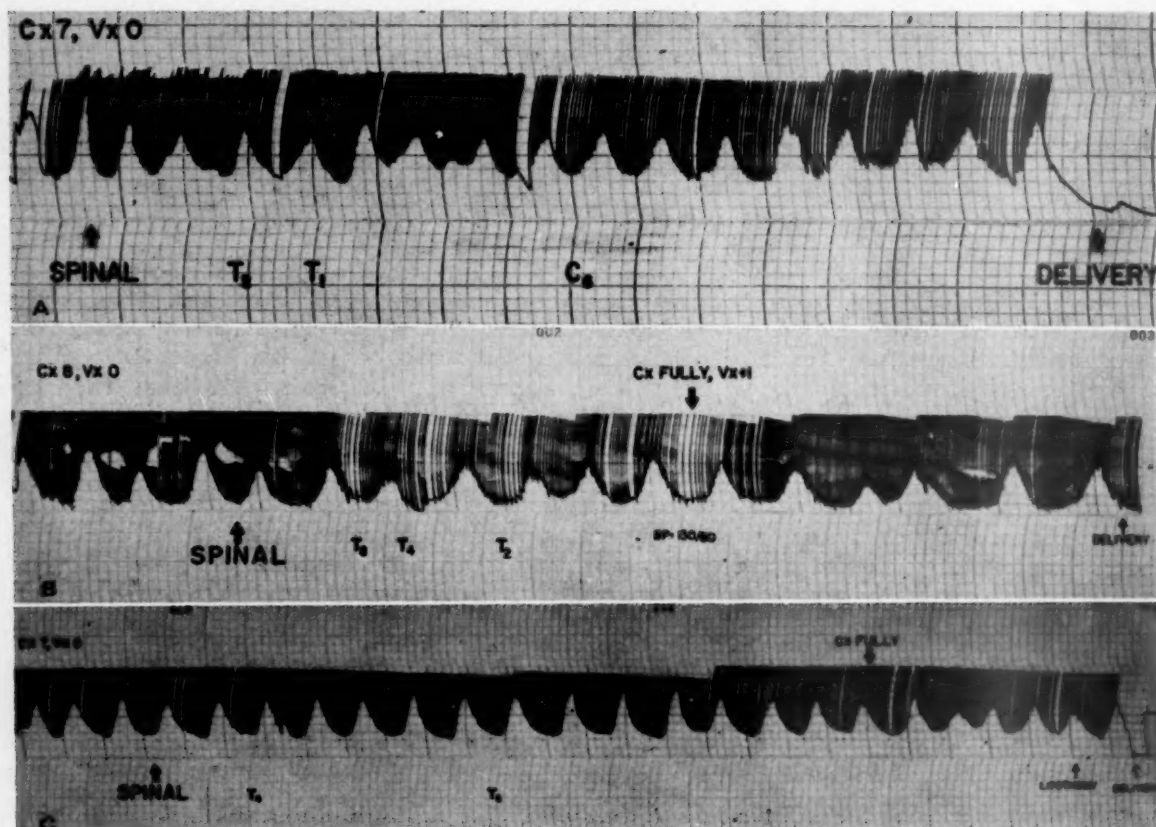


Fig. 2. Uterine contractions before and after high spinal anesthesia with sensory levels in A, C-6; B, T-2; C, T-4. There was no change in intensity, frequency, or tonus.

to 90/60 and then to 60/40. The contractions lost their original intensity and regularity, and frequent small contractions which did not exceed 20 mm. Hg developed. By elevating the lower extremities and using vasotonics and intravenous fluids, the blood pressure was stabilized to 90/60 and the uterine contractions were recorded throughout the rest of the course of labor. During the remaining 90 minutes of labor, although the uterine contractions never resumed the intensity of the preanesthetic level, the cervix dilated from 7 cm. to full dilatation.

A short-lasting but conspicuous alteration of uterine contractions was encountered in another patient (Fig. 4) who was given approximately 2.5 mg. of methoxamine in the intravenous drip of 5 per cent glucose and distilled water because of a short hypotensive episode after the high spinal anesthesia and whose blood pressure rose to 230/130. Almost immediately a uterine contraction

of the intensity of 50 mm. Hg followed the preanesthetic contraction of 40 mm. Hg intensity, and the basal pressure between the contractions was elevated by 12 mm. Hg for a period of 200 seconds. During the 10 minutes of severe hypertension, the frequency was also markedly increased and uterine contractions occurred every 40 seconds. The subsequent contractions even with the high sensory level of anesthesia remained regular in frequency and intensity throughout the labor and delivery. When the anesthetic level was T-2 in comparable patients who did not develop circulatory failure, the uterine contractions were not altered in their intensity, frequency, or tonus.

Sensory anesthesia, T-5 to T-12. Adequate serial recordings of the intra-amniotic pressures were obtained in 17 patients who had sensory anesthesia to the level of T-5 to T-12. The spinal anesthetic was given to these patients when the cervix was at least

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7 cm. dilated. Representative records are shown in Figs. 5A and 5B. One of these patients had polyhydramnios and an anencephalic fetus (Fig. 5A). In no case did we encounter a suppression of uterine contractions or a constant and conspicuous effect

on the intensity or frequency of uterine contractions which could be considered directly related to the spinal anesthetic.

Continuous epidural or continuous caudal anesthesia. The polyethylene catheter was introduced into the epidural space either

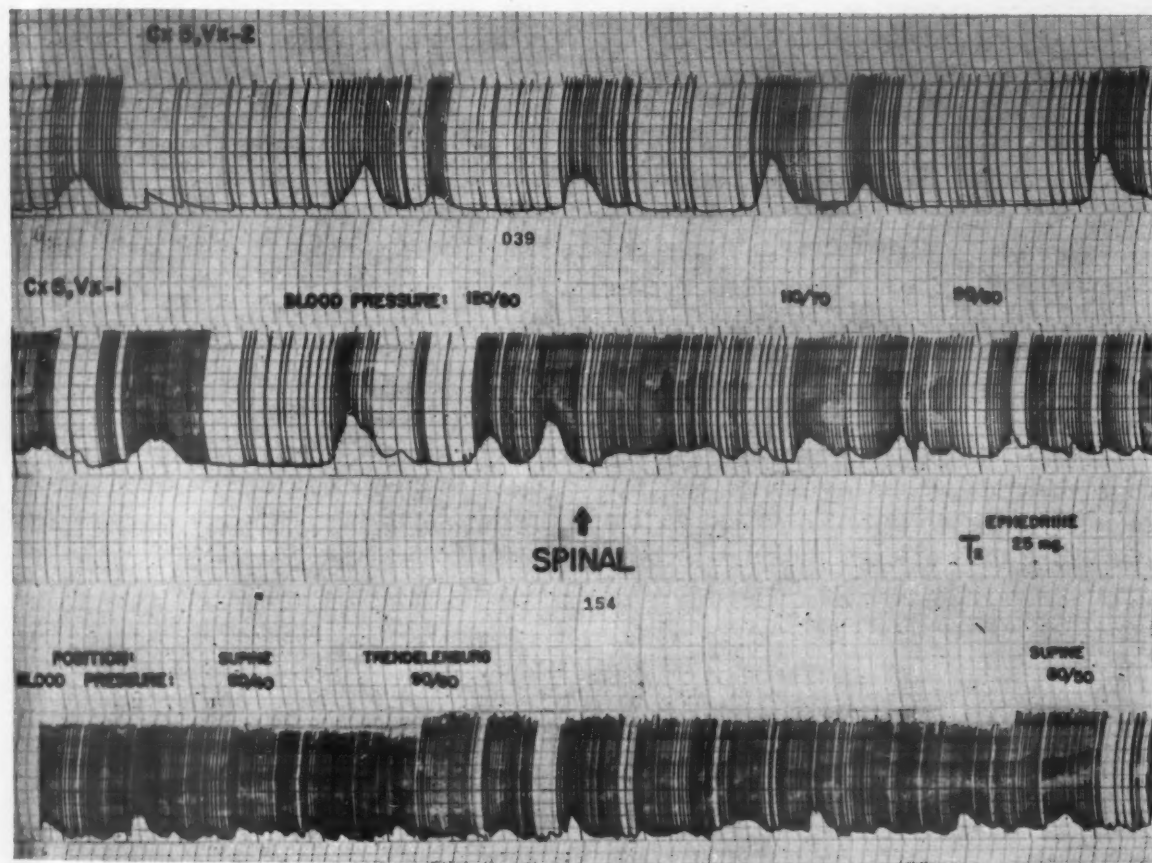


Fig. 3. High spinal anesthesia (sensory level T-2) and acute hypotension. Note the change in the intensity, frequency, and tonus of the uterine contractions.

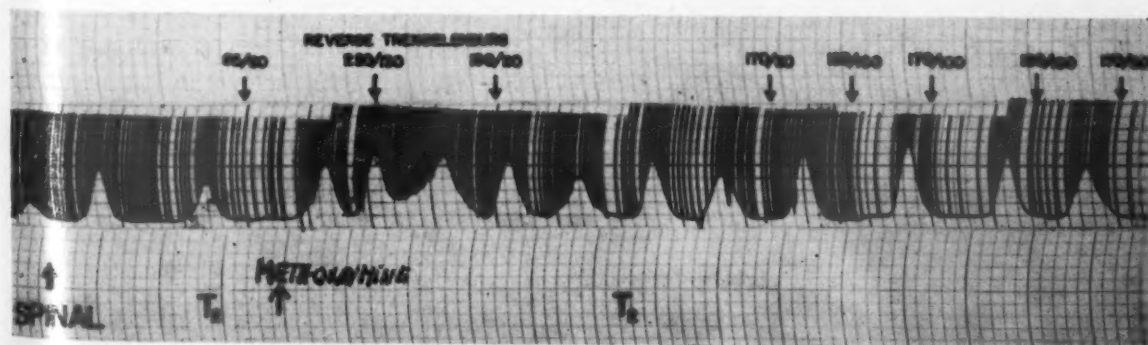


Fig. 4. High spinal anesthesia (T-2) and acute hypertension. The sudden rise in blood pressure was caused by 10 mg. of methoxamine which was added to a 5 per cent glucose and water intravenous drip. It was estimated that approximately 2.5 mg. of methoxamine was used. Note the change in intensity and frequency of the uterine contractions.

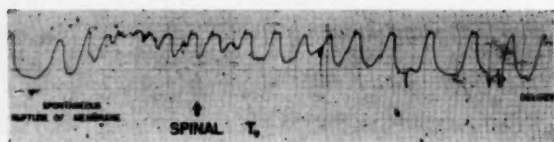


Fig. 5A. Uterine contractions in a patient with polyhydramnios. Note the tetanic contractions following spontaneous rupture of the membranes.

through the lumbar area or through the sacral hiatus, and the amniotic pressures were recorded before and after the injection of the anesthetic in 12 patients. In 3 patients, the anesthetic was injected prior to the induction of labor by oxytocin, and in the remaining 9 patients, the anesthesia was administered during the labor with the cervix dilated anywhere from 2 to 5 cm. Sensory levels were obtained to T-12 as the lowest and T-6 as the highest.

We could not demonstrate that continuous epidural anesthesia resulted in any constant and reproduceable inhibitory or stimulating effect of long duration on uterine contractions. Generally, the uterine contractions with epidural anesthesia as high as T-6 were not altered from their preanesthetic intensity, frequency, or tonus. We did, however, observe interesting temporary inhibitory phenomena in these patients. Immediately after injection of a test dose or anesthetic dose of lidocaine, the intensity of the uterine contractions almost consistently dropped by 10 to 20 mm. Hg. This phenomenon did not last longer than 10, 15, or 30 minutes, and the uterine contractions again resumed the preanesthetic regularity (Fig. 6, A and B).

We also observed stimulation lasting 200 to 300 seconds after the same technique among the patients who were not in labor. Fig. 7 shows the uterine activity in a multiparous patient at term who was not in labor

and who was given epidural anesthesia prior to the induction of labor by oxytocin. When the test dose of anesthetic (5 c.c. of 1.5 per cent lidocaine) was injected into the epidural space, the uterus immediately responded by 4 small uterine contractions. The same phenomenon appeared when the therapeutic dose of the same anesthetic was injected 5 minutes later. An injection of another 5 c.c. of the same anesthetic 15 minutes later resulted in a uterine contraction of 55 mm. Hg intensity although none of the previous contractions were that high.

General anesthesia and uterine contractions. Although the uterine contractions could not be suppressed by spinal anesthesia with the sensory level as high as C-6, in a comparable patient they were almost completely abolished with second plane ether anesthesia (Fig. 8). Twenty patients were studied for the effects of inhalation anesthesia on uterine contractions. In all patients in this group the cervix was completely or almost completely dilated, and the vertex was deeply engaged in the pelvis.

Nitrous oxide. When nitrous oxide was used for the induction of ether anesthesia, no alteration of the uterine contractions was encountered (Figs. 8 and 9, A). When the anesthesia with nitrous oxide plus oxygen alone reached the first plane, the uterine contractions were not conspicuously altered in intensity and had not changed in frequency. The pressures between the uterine contractions were elevated by 5 to 10 mm. Hg.

Cyclopropane. Cyclopropane in its action on uterine contractions is comparable to ether except for its potency in inhibiting the intensity of contractions (Fig. 9, B). When a mixture of 10 per cent cyclopropane and 90 per cent oxygen was used and the patient was brought to the first plane, the uterine

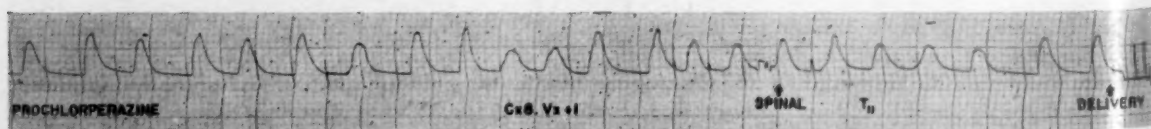


Fig. 5B. Uterine contractions before and after spinal anesthesia with the sensory level to T-11.

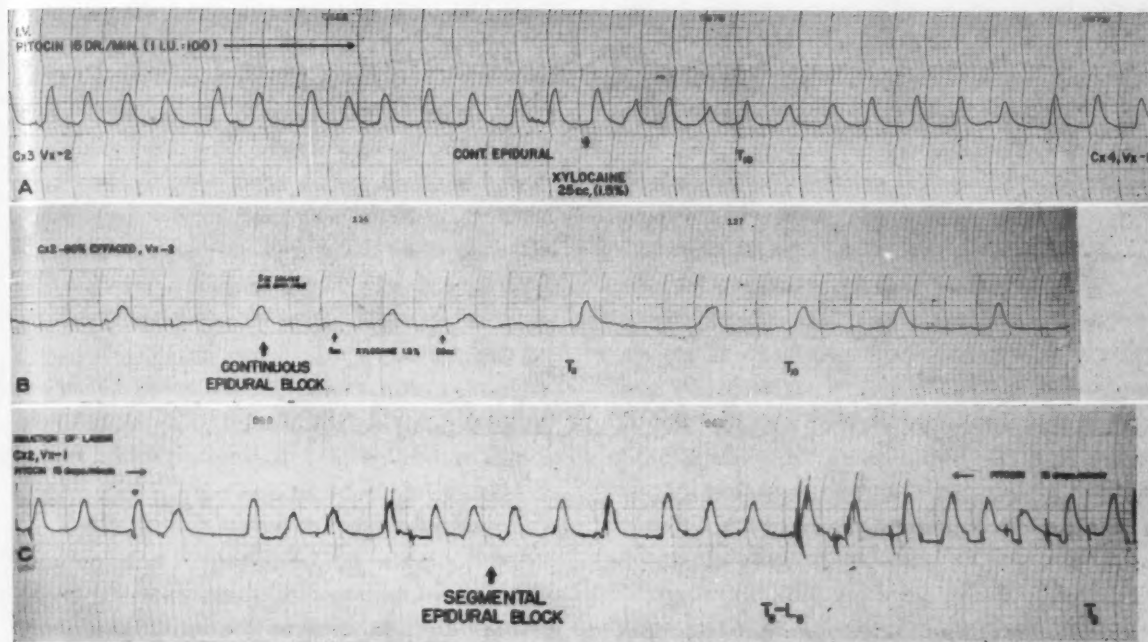


Fig. 6. Continuous epidural block and segmental block. Note the change in the intensity of the uterine contractions following the injection of lidocaine into the epidural space (A and B).

contractions were diminished in intensity by 20 to 30 mm. Hg and continued in the same frequency. When the first plane was maintained for as long as 15 minutes, the uterine contractions were diminished in intensity but increased in frequency. When the cyclopropane was discontinued, the uterine contractions resumed their preanesthetic rhythm.

Ether. Ether alone (open drop) or in combination with nitrous oxide or cyclopropane displayed the most marked inhibitory action on the uterine contractions. It has been possible to demonstrate repeatedly that uterine contractions can be suppressed almost completely by ether anesthesia when the patient is in the second plane. In the first plane of ether anesthesia, the contractions are diminished by 50 per cent (Fig. 9, C) of their preanesthetic level and in the upper second plane by approximately 90 per cent (Fig. 8). In both instances, however, the irritability of the myometrium is revealed by small uterine contractions, which may or may not be of higher frequency than those present during the preanesthesia period. The tonus, i.e., the intra-amniotic pressures between 2 contractions were not altered.

Fluothane. The effect of fluothane on uterine contractions is somewhat similar to that of ether (Fig. 10A). The induction period and the effect of the myometrium is, however, much faster and the recovery rate of the myometrium from fluothane is approximately one half the recovery rate from ether. The intensity of the uterine contractions is markedly diminished with first plane fluothane anesthesia and practically abolished with second plane. The frequency of uterine contractions, not unlike that found with ether anesthesia, however, is also conspicuously altered, suggesting a decrease in the irritability of the myometrium.

Action of exogenous oxytocin (Pitocin) during inhalation and conduction anesthesia. In one patient ether anesthesia was superimposed on uterine contractions which were dependent on oxytocin infusion. The cervix was 2 cm. dilated, the membranes were intact and the vertex was floating. Following 15 minutes of 10 mU. of oxytocin infusion, the uterine contractions became 50 mm. Hg in intensity and occurred approximately every minute. When the oxytocin infusion was stopped, uterine contraction diminished in intensity and became less frequent. While

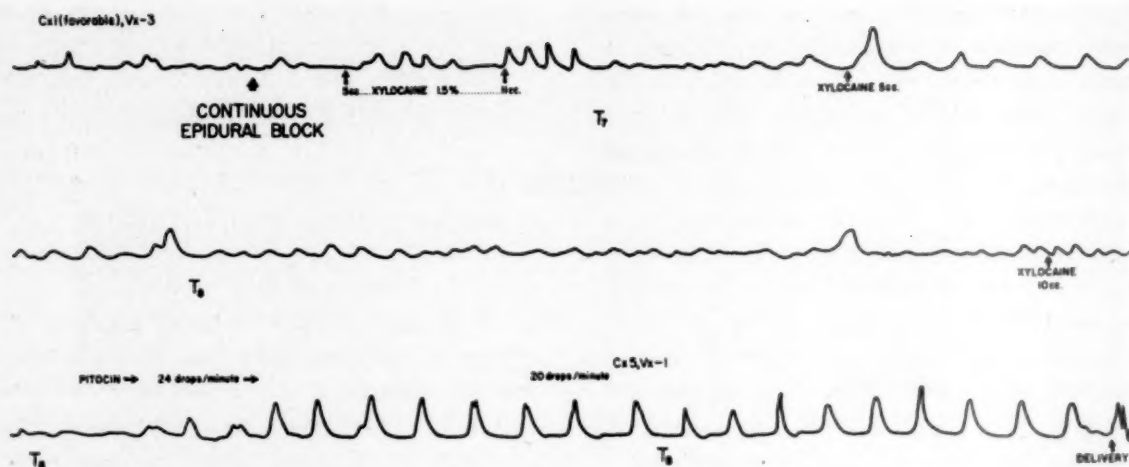


Fig. 7. Short-lasting uterine contractions evoked by the injection of 5 c.c. or 10 c.c. of lidocaine or saline into the epidural space at the level of L-2 in a patient who was not in labor.

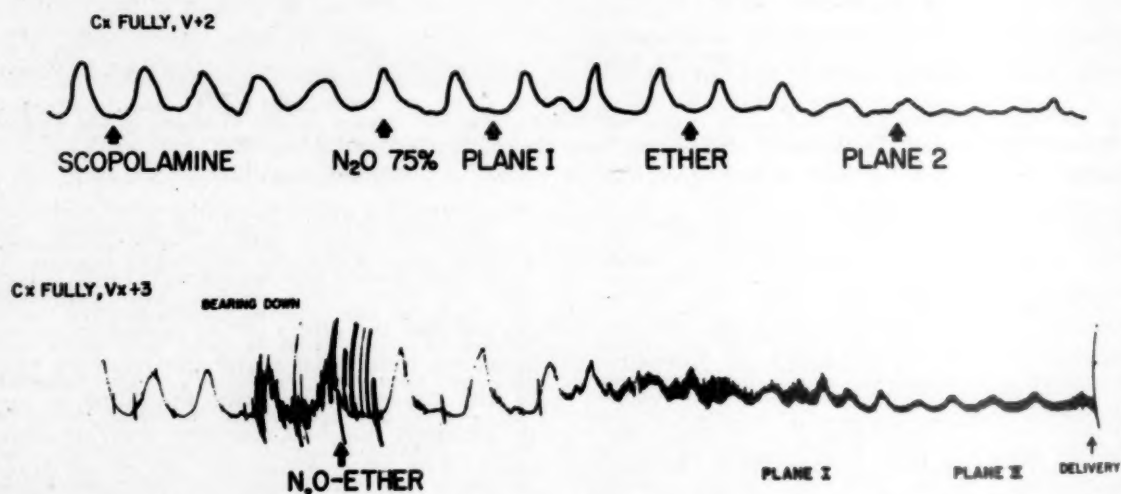


Fig. 8. Uterine contractions are almost completely abolished in the upper second plane of nitrous oxide, oxygen, ether anesthesia.

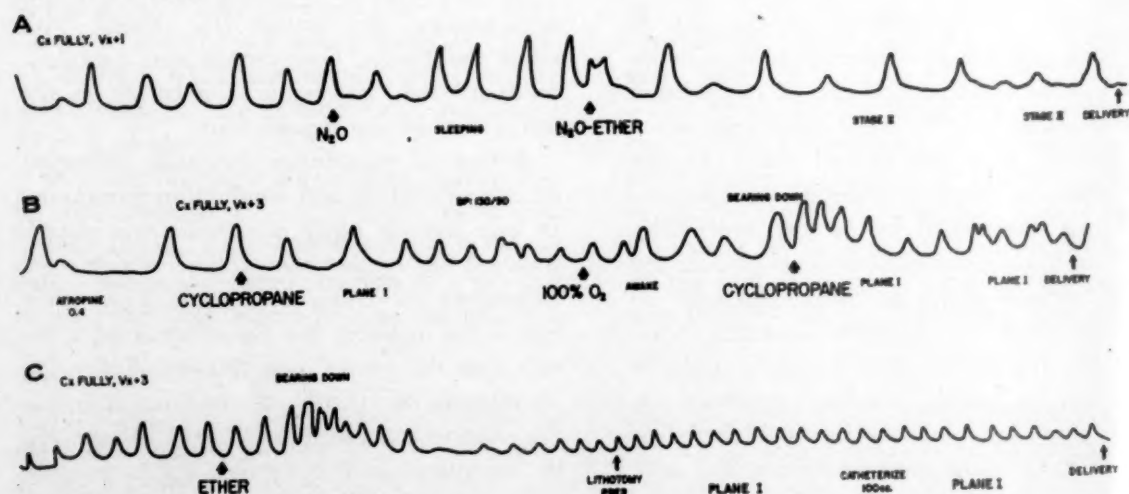


Fig. 9. A, Second stage of N₂O, oxygen ether anesthesia. B, First plane of cyclopropane anesthesia. The patient was awakened (100 per cent oxygen) and 20 minutes later the cyclopropane anesthesia was restarted. C, Ether anesthesia alone.

these contractions by the oxytocin infusion were maintained regular in their intensity, tonus, and frequency, ether anesthesia was given (Fig. 10B) and the patient was brought to the lower first plane. The uterine contractions were completely abolished, but the uterine tonus was not changed for 22 minutes of ether anesthesia. When the 100 per cent oxygen was given and the patient was awakened, the uterine contractions were resumed in frequency almost immediately; however, their intensity was approximately one-half of that during the preanesthetic period. Twenty minutes later the contractions reached the intensity of 50 mm. Hg again. When the uterine contractions were induced and maintained by continuous intravenous oxytocin, conduction anesthesia given simultaneously or prior to the oxytocin induction did not seem to alter the frequency, intensity, or tonus of the uterine contractions, which were dependent on oxytocin.

Comment

The uterine innervation has been anatomically¹⁴ traced from the myometrium of the lower uterine segment through the hypogastric plexus to the second and third lumbar ganglia of the lateral sympathetic chain, but its lumbar or thoracic intraspinal connections with the central nervous system have been proved neither anatomically nor functionally. Keiffer¹⁵ believed that he found ganglionic cells in the muscularis of the low uterine segment and upper portion of the cervix. Recently Krantz¹⁶ revived this study and failed to confirm Keiffer's findings. He observed, however, myelinated and nonmyelinated nervous fibers in their course toward the wall of the vessels. These nerve fibers form a network which makes connections with the Frankenhauser plexus in the broad ligament and continue upward through the sympathetic chains of the hypogastric plexus and through the parasympathetic sacral outflow.

The clinical experience with patients who have had presacral neurectomy, and the experience of anesthesiologists² with patients

who have had saddle block anesthesia gives us sufficient insight into sensory innervation of the uterus, and it is generally agreed that sensory anesthesia to T-10 to T-12 will eliminate pain from the uterus, pelvic floor, perineum, and vulva. Nothing is literally known, however, about the uterine motor innervation and its function in relation to uterine contractility during labor.

We do not claim to answer this problem on the basis of this study, but some interesting phenomena which occurred during the course of our observations of uterine contractility under conduction anesthesia deserve comments. It has been shown here that reflex uterine contractions can be induced by stimulating the spinal cord by mechanical distention of the epidural space at the vertebral levels of L-3 to L-1 in a patient who was not in labor. Similarly, using the same technique of spinal cord stimulation, it has been demonstrated, almost consistently, that an inhibiting effect of short duration (10 to 15 minutes) can be seen on uterine contractions among patients who are in labor. These stimulating or inhibiting effects on the uterus are abolished when the injected anesthetic is absorbed and the local epidural pressure is released. When the anesthetic was injected directly into the subarachnoid space at any level, no alteration of uterine contractions was observed. Neither was a conspicuous change in uterine contractility noticed when the anesthesia sensory levels were as high as T-2 and C-6.

It has been well documented by others¹⁸ that a strip of myometrium from the pregnant uterus in vitro will exhibit uterine contractions, that patients who had undergone the resection of hypogastric superior nerves¹⁷ have regular and painless labor, that patients in whom the spinal cord had been transected¹⁸ developed spontaneous labor, and that even the isolated pregnant uterus is capable of expelling the fetus.¹⁹

Thus the uterine contractility during labor must be considered autonomous. Yet the uterine response to the stimulation of the spinal cord not only bears out the presence of motor fibers in the spinal cord, but

it also seems to point out that the motor innervation possesses certain specific functions which are related to the amplitude and frequency of the uterine contractions. Reflex contractions can be produced by stimulation of the spinal cord in a quiescent uterus and regular contractions can be slightly inhibited in a contracting uterus. This is not sufficient evidence for any definite conclusions, but it suggests that the motor innervation is capable of modifying uterine contractility in both directions, i.e., stimulating and inhibiting.

Are then these modifying effects of motor innervation mediated by nervous impulses transmitted directly to the contractile system of the cell or through their effect on release of oxytocin, or is the effect of motor innervation on the uterine contractions exerted primarily through its action on the blood vessels and the subsequent changes in the blood flow?

In our experimental study, uterine contractility was not altered by spinal anesthesia alone, i.e., when all spinal and paraspinal pathways were interrupted. The blockade of the nerve impulses per se would not seem to change uterine movements. However, uterine contractions were almost completely inhibited when moderately severe hypotension developed, and they were stimulated when a severe acute hypertension ensued.

The effect of the uterine blood flow on the uterine contractions has been a subject of controversy for a long time. In 1879, Roehrig²⁰ found that clamping of the aorta sufficed to induce strong uterine contractions. Robson and Schild²¹ on the basis of their experiments came to the conclusion that uterine activity and blood flow vary independently. Reynolds¹³ feels that generally a fall of blood pressure is associated with an increase in frequency and amplitude of contractions and a rise in blood pressure has an opposite effect as well as an increase in tone. Caldeyro-Barcia²² encountered a change in uterine contractions by changing the position of the patient.

Our own observations would indicate that uterine contractility varies with acute and

severe hemodynamic changes. It should be pointed out that severe alterations of blood pressure in our experiments were accidental and neither was the uterine blood flow measured, nor could objective evidence of the increase or decrease of uterine blood flow under these conditions be more specifically elicited. Precisely how the uterine blood flow changes with these abrupt alterations of systemic blood flow is not known, but in general an acute hypotension is thought to be associated with a decrease in uterine blood flow and the reverse is considered true in an acute hypertension, at least in its initial stage.

It is likely that all high spinal anesthetics affect the uterine blood flow, but not all patients with the same sensory level, e.g., T-1 and the same degree of hemodynamic change will necessarily always show the same quantitative change in the uterine contractility. Those patients, however, who with this height of sensory anesthesia do develop hypotension will likely also show a conspicuous change in the intensity and frequency of uterine contractions.

Clearly then, if noncomplicated spinal anesthesia with the sensory level to C-6 and T-1 to T-2 has no effect on the uterine contractions and if the same level of spinal anesthesia with acute hypotension results in an alteration of the frequency and intensity of uterine contractions, the uterine contractility is more susceptible to the changes in blood flow than to the inhibition of other functions which the motor innervation may possess at the cellular level. This is understandable in view of the known cellular mechanisms of uterine contractility. The functional contractile system of the actomyosin, ATP, and ions was demonstrated to contract *in vitro*.²³ Individual constituents of this system can be deranged by severe changes in the uterine blood flow, but the depletion of actomyosin or energy supply is usually not instantaneous.

Changes of cellular membrane potential associated with the ratio of extracellular and intracellular potassium also are relatively slow processes. Oxytocic activity of

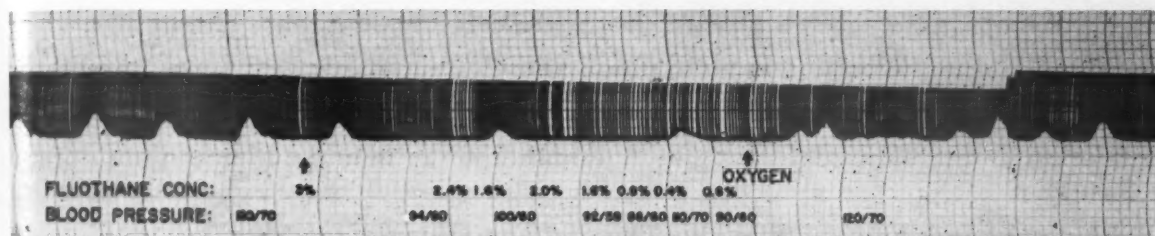


Fig. 10A. Fluothane anesthesia. Note the change in intensity and frequency of the uterine contractions.

the serum may possibly vary simultaneously with the rate of blood flow. It has been documented that the rate of oxytocin clearance may play an important part in the contractile mechanism.²⁴ Perhaps the most susceptible component of this system is oxygen tension, which is known to vary instantly with the alteration in blood flow. The interrelation of anaerobic enzymatic processes in the myometrium and aerobic metabolism in regard to uterine contractility is, however, not known, and any suggestion in this respect would be purely conjectural. There is no evidence that an acute blockage of the neuropathways of uterine innervation alone could derange any of these basic mechanisms of uterine contractility. On the other hand, if systemic hemodynamic changes develop following the blockage of sympathetic and parasympathetic nervous system, and if the uterine blood flow is altered markedly and for a sufficient period of time, the cellular contractile system seems to be affected and the uterine contractions clinically altered.

Although our experiments suggest that the effect of motor innervation upon uterine contractility is primarily mediated through the effect on uterine blood vessels and uterine blood flow, there is sufficient evidence in the literature to show that trophic disturbances of the myometrium develop following surgical sympathectomy. Simeone and Ross²⁵

observed a decrease in resistance of the myometrium against distention and stretch following sympathectomy in pregnant cats. A decrease in uterine tone was encountered and even spontaneous rupture of the pregnant uterus occurred.

Abou-Shabanah, Ullery, and Wenger,²⁶ in their experiments on sympathectomized and parasympathectomized pregnant dogs, made somewhat similar observations on the relaxation and hypotonicity of the uterine cervix. They attributed this phenomenon to the dissection of the sacral outflow, which they consider to be the pathway of the uterine motor innervation.

Sympathicolysis or parasympathicolysis, which is attained by high spinal anesthesia with the sensory level to C-6 and T-1 to T-2 in its physiologic action is similar to surgical sympathectomy and parasympathectomy. The pharmacologic action which blocks the sympathetic rami communicantes and sympathetic ganglia, however, is of short duration and no chronic effects of spinal anesthesia on the function or on the tissue could be expected.

Effects on uterine contractions and uterine tone comparable to those obtained after surgical sympathectomy are not demonstrable in our experiments. It is conceivable, however, that a chronic absence of the sympathetic and parasympathetic innervation would exhibit trophic disturbances of

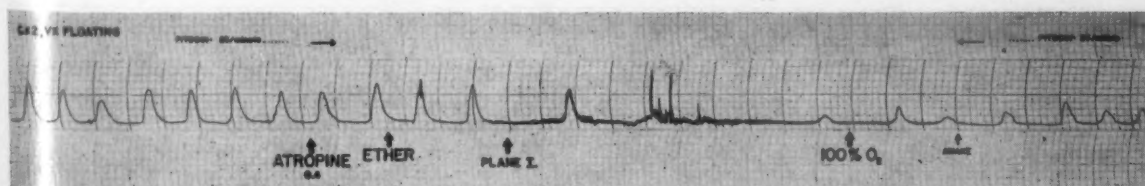


Fig. 10B. Ether anesthesia with simultaneous intravenous infusion of oxytocin, 26 drops per minute.

the myometrium, and this would result in a decreased resistance against distention and stretch, that is, a decrease in uterine tone.

Summary

On the basis of the presented observations, it is suggested that the spinal connections with the motor innervation of the uterus exist in the upper lumbar regions. Furthermore, it is evident that the uterine contractions can be initiated and/or maintained in the term pregnant uterus which has been denervated by spinal anesthesia with the sensory level as high as C-6. Acute sympathetic blockade induced by high spinal anesthesia did not exhibit a demonstrable effect on uterine contractility or tonus during labor, as long as the hemodynamics in the patient were not altered. A demonstrable alteration of the intensity, frequency, and tone of uterine contraction was recorded in association with changes in the blood flow, i.e., in shock or in acute, transient, induced hypertension. It is suggested that the primary function of the motor innervation during labor is the vasoregulatory, and the secondary function is the maintenance of the physiologic balance of trophic processes in the myometrium. What precisely are the pathways of motor innervation and what are its functions in relation to the onset of labor is the subject of our current study.

The use of spinal anesthesia, continuous epidural or caudal anesthesia did not have any conspicuous qualitative effect on the uterine response to oxytocin, either during the labor or when the labor was induced and oxytocin was injected after the spinal anesthetic had been given.

Although the uterine contractions in this series were not abolished by high spinal anesthesia, they were promptly inhibited by

inhalation anesthesia and almost completely abolished during the second plane of the nitrous oxide ether anesthesia. Whether ether acts centrally and effects the release of oxytocics from the hypothalamus or posterior pituitary, or whether ether acts directly on the myometrium or its enzyme system (oxytocinase) can be only partially answered. Our experiment on the effect of ether on uterine contractions during the intravenous oxytocin infusion points out that the effect of ether is likely that on the target organ, i.e., on the myometrium rather than on endogenous and/or exogenous oxytocin. These findings are consistent with those reported on the effect of ether on the myometrium of the pregnant uterus *in vitro*.²⁷

Conclusions

1. The effect of conduction and inhalation anesthesia on uterine contractions was studied by serial recordings of the intra-amniotic pressures of 60 normal patients.

2. Spinal anesthesia with the sensory level as high as C-6 and T-2 did not inhibit the uterine contractions.

3. The uterine contractions were almost completely abolished during the lower first plane and upper second plane of nitrous oxide ether anesthesia.

4. Uterine contractions dependent on intravenous oxytocin stimulation were completely abolished by ether anesthesia.

5. Spinal anesthesia, or continuous epidural anesthesia, did not interfere with the induction or maintenance of uterine contractions by oxytocin.

6. In pregnancy at term, stimulating effects on the quiescent uterus and short-lasting inhibitory effects on the uterine contractions have been elicited by mechanical stimulation of the spinal cord at the levels of L-3 to L-1.

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Uterine contractions during labor in myotonic muscular dystrophy

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THE purpose of this paper is to present some observations on the uterine contractions during labor in a patient with myotonic muscular dystrophy.

Review

Myotonic muscular dystrophy (dystrophia myotonica, myotonia atrophica) is a rare degenerative disease of the neuromuscular system characterized by (1) muscular atrophy, primarily involving the muscles of the neck and face; (2) myotonia, involving these and other voluntary muscles not affected by atrophy; and (3) dystrophic changes, including cataracts, early baldness, electrocardiographic changes, gonadal atrophy, and evidence of dysfunction of other endocrine glands.^{1, 2} The disease follows a hereditary pattern and is more common in the male sex. The incidence of this rare disease is not accurately known.³

The most pronounced symptom is an inability to relax the grasp properly. Myotonia refers to an abnormally delayed relaxation of contracted skeletal muscle, and after the muscle is released from nervous stimulation the muscular contraction continues for several seconds. In myotonic muscular dystrophy (as opposed to myasthenia gravis) there is an increase in the excitability of the muscles, producing a tetanic contraction; quinine has a curare-like effect

and decreases the muscular excitability, while neostigmine and potassium produce the opposite effect. Electromyographical studies of the myotonic skeletal muscles, originally described by Erb in 1886,⁴ showed that stimulation by a galvanic current produced a tonic sluggish contraction, slowly subsiding after the current is withdrawn (myotonic reaction).

No characteristic pathological lesions of the neuromuscular system are present although Wohlfart³ has shown that histologically the myofibrils of the skeletal muscle are often destroyed with a corresponding decrease in the sarcoplasm content, and Maas⁵ has noted that almost all the body tissues show degenerative changes when examined microscopically.

In the male "atrophy of the testicles is common and the patient usually loses his sexual desire and becomes impotent by age 25 or 30. Similar changes occur in the female and are associated with amenorrhea."¹ Aggravation of myotonia in women during menstruation and pregnancy and improvement after delivery has been reported.⁶ In Thomassen's study⁷ of 33 women between the ages of 15 and 50 there were "menstrual irregularities more frequently found in women with severe degrees of muscle dystrophy." In this group there was a high proportion of unmarried women, but 12 of these patients have been delivered of 24 children. It is stated that there is no reduced fertility in marriages in which one partner has myotonic muscular dystrophy,

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but, commonly, only the least affected patients ever produce children. Urinary estrogens were studied in 3 of these women with hypomenorrhea, and estrogen excretion was found to be decreased. Davis⁸ has described a "normal pregnancy and delivery of a normal infant occurring in a patient suffering from dystrophia myotonica," but nothing is stated as to the details of labor in this and previous studies.⁹

Since there are no specific observations on the course of labor and on the character of the uterine contractions in these patients, we would like to present the following case history:

Case report

A 28-year-old unmarried Negro woman, gravida iii, para ii, was admitted to the Medical Service on Feb. 25, 1959, complaining of exertional dyspnea, orthopnea, and palpitations of 4 weeks' duration. Her menstrual periods had always been regular (every 28 days) but heavy, lasting 8 or 9 days. Her last menstrual period was Nov. 28, 1958, and the expected date of confinement was Sept. 4, 1959. Family history revealed both her parents and all siblings alive in North Carolina and without known systemic disease. She gave a documented history of syphilis 10 years before, treated with penicillin, and had noted recurrent episodes of herpes simplex. She described two previous spontaneous uncomplicated full-term vaginal deliveries at home in North Carolina, resulting in the births of a 9½ pound female and an 8½ pound male infant. We have no information on these children.

Physical examination revealed a small left preauricular nodule, mild gingivitis, and erythema multiforme of the right forearm. The cardiac rhythm was irregular, with an apical systolic murmur and an intermittent third sound. The uterus was 12 weeks in size.

The hemoglobin level was 9.1 Gm.; Mazzini test, 4-plus; Kolmer test, negative; PBI level, 5.9. Electrocardiogram revealed atrial flutter with a varying atrioventricular block.

During an attempted quinidine conversion on March 13, 1959, after a total dosage of 0.8 mg. of quinidine, the patient had a cardiac arrest which responded to vigorous pounding of the chest. Four hours later the patient sustained a second episode of cardiac arrest, necessitating emergency thoracotomy and cardiac massage

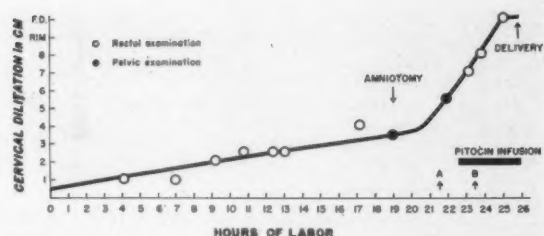


Fig. 1. Cervical dilatation time graph showing Points A and B where tocodynamometer tracings were taken of uterine contractions.

(the estimated period of cardiac standstill was 6½ minutes). Following defibrillation the heart was in normal rhythm. At this time the patient was 15 weeks from the onset of her last menstrual period. She made a good recovery from this episode.

She was then followed in the Ante-Partum Clinic, but was admitted to the Obstetrical Service on June 3, 1959, because of an episode of syncope. Electrocardiogram revealed sinus arrhythmia with sinus bradycardia and incomplete atrioventricular block.

A history was then elicited of difficulty in opening a closed fist, worse in the past year, and progressive difficulty in seeing out of the right eye. Neurological examination revealed "hatchet facies" and temporal muscle atrophy. There were myotonia, bilaterally, of both the hand muscles and weakness of all the muscles of the upper extremities, neck, and shoulder girdle. Subcapsular opacities of the right eye were present. There was no baldness. Laboratory findings included a PBI level of 8.3, total cholesterol, 208, and creatinine excretion 834 mg. per 24 hours. Electrocardiogram revealed a normal sinus rhythm, and electromyographic findings were consistent with primary muscle disease of the type seen with myotonic muscular dystrophy. The urinary 17-ketosteroid level was 7.0 mg. per day with ketogenic steroids 9.5 mg. per day. Following an intravenous infusion of 25 units of ACTH, the 17-ketosteroid level was 17.1 mg. per day and ketogenic steroids 24.2 mg. per day.

On Sept. 21, 1959, the patient went into labor, and, following a total labor of 25 hours and 53 minutes, with oxytocin stimulation for 2 hours, she had a spontaneous delivery of a 3,380 gram living male infant from the occipito-anterior position under caudal anesthesia. Medication during the first stage consisted of secobarbital 100 mg., prochlorperazine dimaleate 10 mg., meperidine 75 mg., and atropine 0.2 mg.;

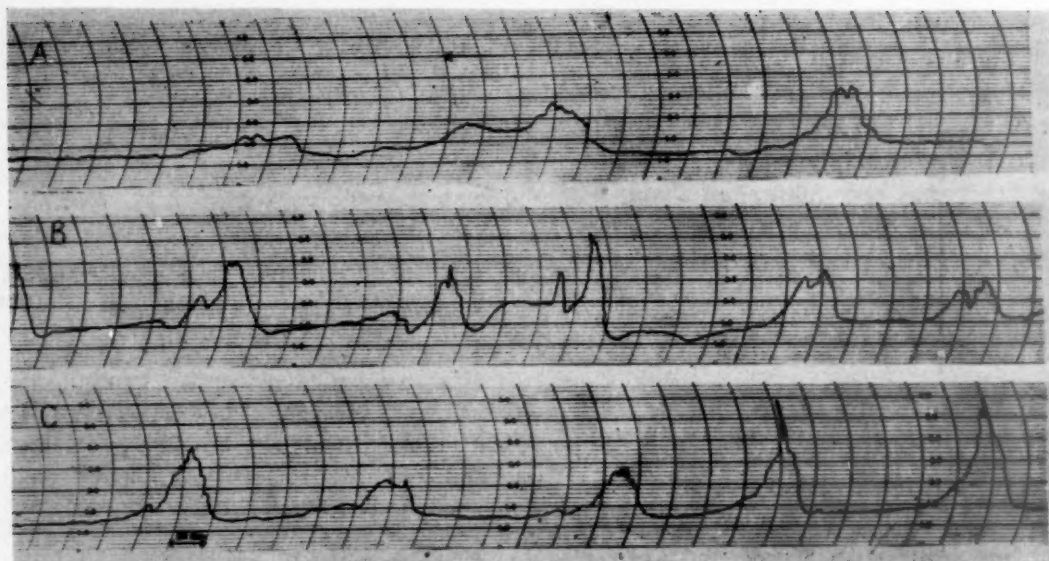


Fig. 2. Comparison of tocodynamometer tracings during the first stage of labor before and after oxytocin stimulation (Points A and B in Fig. 1). A, Graphic form of the clinically prolonged relaxation phase; B, the shortened relaxation phase following oxytocin stimulation; C, uterine contractions of a normal multipara in the first stage of labor, shown for comparison.

at no time was the patient considered to be under heavy sedation. The infant was normal (Apgar score 6) except for bilateral club feet. A graphic analysis of this patient's labor is shown in Fig. 1 along with a discussion of the observed uterine contractions (Fig. 2).

The postpartum course was normal until the tenth day when bilateral pyelonephritis due to a hemolytic *Escherichia coli* developed. This responded to chloramphenicol therapy. Lactation was noted.

Clinically, the myotonic muscular dystrophy has remained unchanged since the pregnancy.

Comment

Since we were unable to locate any previous observations on the character of the uterine contractions in labor in myotonic muscular dystrophy, we shall present our observations on this patient. The total labor (Fig. 1) was 25 hours and 53 minutes, with a first stage of 25 hours and a second stage of 50 minutes. Early in the first stage of labor it was noted that the uterine contractions were relatively mild in intensity and clinically of prolonged duration.

For this reason, tracings of the uterine contractions were made with a tocody-

namometer* (Fig. 2). A representative section of the record is reproduced (A) suggesting that the time interval from the peak of the contraction to complete relaxation is somewhat prolonged. The central contraction with the plateau type of relaxation was the most frequently encountered pattern. The second tracing shown (B) was taken following an oxytocin infusion introduced for stimulation of labor. A representative contraction here shows a higher amplitude and shortened relaxation time, approximating that of a normal multipara, (C) shown for comparison.

An over-all reconstruction of this patient's labor is shown in the cervical dilatation time graph (Fig. 1). Friedman,¹¹ in a study of 500 multiparous labors, has established limits of normality, and comparison of the cervical dilatation time curve with the "ideal" sigmoid curve of the uncomplicated multiparous patient reveals a normal progression of cervical dilatation.¹² The clin-

*The apparatus consists of a Statham strain gauge mounted on a brass ring connected through a suitable resistance bridge and amplifier to an Esterline-Angus recorder.¹⁰

ical impression, however, was that of an inert labor prior to the onset of oxytocin stimulation.

We do not plan to offer an explanation or to formulate any conclusions from our observations on this patient but, because of the developing evidence that myotonic muscular dystrophy may involve the non-skeletal muscular tissues,^{3, 5} notably cardiac muscle,^{13, 14} and since cardiac muscle and uterine muscle may be physiologically related, the clinically abnormal uterine contraction pattern noted in this patient may be a manifestation of the generalized disease. The uterine contractions observed before oxytocin stimulation suggested a relationship to the tonic contractions with prolonged relaxation observed in skeletal muscle in myotonic muscular dystrophy. The character of these contractions appeared to be changed by oxytocin stimulation, in that the relaxation time was shortened and a more "normal" type of contraction was then produced. That car-

diac abnormalities also occurred in this patient is of interest, and these will be reported in a subsequent publication.

Endocrine studies failed to reveal any endocrine hypofunction.

Summary

Graphic tracings representing uterine contractions during labor in a patient with myotonic muscular dystrophy are presented. The patient had a clinically inert labor requiring oxytocin stimulation and tocodynamometer tracings taken before and after stimulation are compared. The graphic representation of the uterine contractions suggested a prolonged plateau phase of relaxation, which had not been previously reported, and this relaxation phase appeared to be shortened by the oxytocin stimulation.

This is also a case of cardiac arrest at 15 weeks' gestation, with survival of mother and delivery of an apparently normal infant.

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Afibrinogenemia in early spontaneous abortion

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THE relationship between the depletion of circulating fibrinogen and hemorrhage in obstetrics is now well established and many cases of hypofibrinogenemia or afibrinogenemia, accompanied by very severe hemorrhage in a variety of obstetrical conditions, have been reported in the last decade.¹⁻⁴ The main obstetrical conditions in which alterations of the coagulation mechanism are more likely to occur are: (a) premature separation of the placenta (abruptio placentae), (b) amniotic fluid infusion, (c) long-standing intrauterine retention of a dead fetus.

Less appears to be known about fibrinogen depletion in abortions. Some reports have been published of hemorrhagic complications in missed abortion in the late months of pregnancy and in abortions with severe local or generalized infection.^{2, 4}

To the best of our knowledge, no reference has been made to hypofibrinogenemia or afibrinogenemia occurring in a spontaneous abortion in the ninth week of gestation.

Case report

A 29-year-old mother of 7 children, who had been married for 11 years, gave a history of 7 pregnancies, 7 normal births, and no abortions. The date of the last menses was Oct. 12, 1959. Shortly afterward the patient was seen in our clinic because of abdominal and low back pain. An Aschheim-Zondek test, performed on Dec. 9, 1959, resulted in 5,000 hyperemic units positive and the suspicion of pregnancy was thereby confirmed. Ten days prior to admission, spot

bleeding from the vagina was observed. This increased progressively and there was deterioration in the patient's general condition. The examination in the outpatient clinic led to the diagnosis of spontaneous abortion, and on Jan. 3, 1960, the patient was hospitalized. Physical examination revealed a woman in fair condition. Blood pressure was 120/70; pulse rate was 80 per minute. The abdomen was free of masses.

The external genitals showed no abnormalities. On bimanual palpation, an enlarged uterus, corresponding to 9 weeks of pregnancy, was found. The cervix was dilated 2.5 cm. and the placenta was felt protruding into it. Blood was oozing from the uterus. The adnexa and the cul-de-sac were free. The Aschheim-Zondek test was found to be 500 hyperemic units negative. The clinical findings and the Aschheim-Zondek test confirmed the diagnosis of spontaneous abortion.

On Jan. 4, 1960, a curettage was done. During the procedure marked bleeding from the uterus occurred and it was necessary to give the patient a blood transfusion. She received 400 c.c. of carefully cross-matched whole citrated blood (Group B, Rh positive). In addition, oxytocins were administered with a beneficial effect on the uterine contractions. The uterine content was sent for histological examination, which confirmed the diagnosis of early abortion.

Four hours after the curettage, severe bleeding from the uterus again occurred and peripheral circulatory collapse followed. The blood pressure could not be determined. The pulse rate was 160 per minute. About 700 c.c. of whole citrated blood was given under pressure and the systolic blood pressure rose to 75 mm. Hg. The patient continued to bleed. No clot was formed in the whole blood coagulation test after 45 minutes. Assay of blood fibrinogen by clotting with a solution of thrombin confirmed the total absence of fibrinogen. Further tests did not reveal the presence of abnormal fibrinolytic activity.

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The patient was given 2 Gm. of fibrinogen (human) intravenously and the hemorrhage promptly stopped. The blood pressure, however, remained low and an infusion of phenylephrine was commenced. The blood pressure gradually rose to the level of 105/75 mm. Hg and the patient's general condition improved. At the end of 2 hours the bleeding started afresh. Whole blood coagulation time was now found to be 45 minutes; the clot was friable. An additional 2 Gm. of fibrinogen was administered, followed again by cessation of bleeding and an improvement in the patient's well-being. Cortisone, penicillin, streptomycin, and chloramphenicol were also administered. The blood examination revealed a hemoglobin level of 12 Gm. per cent and a leukocyte count of 9,600 with a normal distribution. The blood pressure was unstable and it was necessary to continue the phenylephrine drip. Results of chemical examinations at this stage were: urea 61 mg. per cent, chloride 100 mEq. per liter, sodium 125 mEq. per liter, potassium 3.4 mEq. per liter. After 48 hours, the phenylephrine drip was discontinued.

The following day (Jan. 7, 1960), the blood tests gave the following values: hemoglobin level 13.2 Gm. per cent; red blood cell count 4.7 million; reticulocytes 1.4 per cent; platelet count 85,000; bleeding time 5 minutes; whole blood coagulation time 10 minutes with formation of a firm clot. The white cell count was 22,000, with 84 per cent neutrophil polymorphonuclear cells, 15 per cent band forms, 1 per cent monocytes. The patient's condition had improved markedly. The blood pressure was now stable at 115/75 mm. Hg.

Results of blood tests on Jan. 10, 1960, were: hemoglobin level 12.5 Gm. per cent; red blood cell count 4.3 million; white blood cell count 9,700, with a normal differential formula; platelet count was 132,000; bleeding time 3 minutes; and coagulation time 9 minutes. Blood urea, electrolytes, and liver function tests were normal. The plasma fibrinogen level was 420 mg. per 100 ml. Urinalysis was negative. Temperature was normal; pulse rate was 90 per minute. The antibiotic therapy was stopped and the patient was discharged.

Comment

In the pertinent literature only 10 cases of hypofibrinogenemia or afibrinogenemia associated with abortion have been mentioned (Table I). The table does not include the

cases of Longo,¹² since this author did not present any clinical data. The case recorded by Soulier and associates⁵ occurred following the intrauterine injection of potassium hypochlorite. The resulting afibrinogenemia was attributed to a fibrinolysin. This patient was observed to have severe hemolysis, but no circulating anticoagulant could be detected.

As seen from Table I, most cases of hypofibrinogenemia or afibrinogenemia occurring in abortion are accompanied by either circulatory collapse or localized or generalized infection. The causes of coagulation disturbances in infected abortion are, as yet, incompletely understood. According to Murphy,¹³ the infection brings about an increased hemolysis and a fall in the number of circulating platelets. In the case of septic abortion presented by Conley and associates² the disturbances in blood coagulation were primarily due to extensive liver dysfunction.

The high mortality rate in the series presented in Table I is most commonly due to shock and infection following the afibrinogenemia.

In our case the afibrinogenemia of early spontaneous abortion occurred 3 to 4 hours after the curettage. No disturbed liver function was observed by clinical or laboratory tests. Similarly, no signs of hemolysis were detected. The fibrinolytic activity was not increased. As this was an early abortion, the conditions for an amniotic fluid accumulation did not obtain. In the cases of late missed abortions, the afibrinogenemia may be caused by a mechanism operative in long-standing retention of a dead fetus in the uterus, described by Hodgkinson and co-workers,¹⁴ the continuous accumulation of amniotic fluid being responsible for the fibrinogen depletion and its consequences.

Friedman and Anderson⁹ propounded that the mechanism of the afibrinogenemia in their case was similar to that seen in abruptio placentae in a more advanced gestation. This does not apply in our own case, considering the shortness of gestation (9 weeks) and the histological picture of the uterine curettings. One should not overlook the fact that human

Table I. Cases of abortion complicated by fibrinogen depletion

Name of author	Year of publication	State of patient	Type of abortion	Complications	Remarks
Conley et al. ²	1950	Died	Septic	Acute yellow atrophy bacteremia	
Weiner et al. ³	1950	Alive	Late missed abortion		Long-standing intra-uterine retention of a dead fetus; Rh incompatibility; subtotal hysterectomy
Soulier et al. ⁵	1952	Died	Late missed abortion	Placenta adherens; manual removal of placenta	Rh incompatibility
Mayer et al. ⁶	1954	Died	Late missed abortion	Placenta adherens; manual removal of placenta	Rh incompatibility
Jackson et al. ⁷	1955	Died	Late missed abortion	Shock; fetus maceratus	
Pritchard ⁴	1956	Died	Infected traumatic abortion	Septicemia (<i>Clostridium welchii</i> , type B)	
Stouffer ⁸	1958	Alive	Missed abortion with evacuation of mummified fetus		Long-standing intra-uterine retention of a dead fetus
Friedman and Anderson ⁹	1958	Alive	Incomplete abortion 4th month	Shock	
Gollub ¹⁰	1959	Died	Late abortion 6th month	Shock	
Fuchs ¹¹	1959	Alive	Late missed abortion		Long-standing intra-uterine retention of a dead fetus

placenta and decidua have a very high thromboplastin content.¹⁵

Schneider^{16, 17} advances the hypothesis that the tissue thromboplastin of the placenta and the decidua enters the maternal blood streams and gives rise to the intravascular transformation of the fibrinogen into fibrin. This theory is capable of explaining both the diminished fibrinogen content of the blood and the initial shock state.¹⁸ It should also be noted that in operations on other tissues rich in thromboplastin, e.g., lung, severe hemorrhages due to fibrinogen depletion have been described.^{19, 20} It is possible that, during abortion, placental and decidual thromboplastin find their way into the maternal circulation and subsequently lead to afibrinogenemia.

Schneider,²¹ in addition, described tears in the basal layer of the decidua in 2 cases

of early separation of the placenta, subsequently subjected to histological examination.

In cases of incomplete abortion, curettage is routinely performed to clean the lacerated uterus of all tissue shreds. The surgical trauma in curettage is too small to be considered per se a factor leading to afibrinogenemia. However, the lacerations caused by the curettage may be sufficient to enable thromboplastin to enter the circulating blood.

The specific treatment for afibrinogenemia is administration of fibrinogen, which replaces the deficient body stores and the coagulation mechanism is thus reactivated. However, the commonly occurring complication of afibrinogenemia, viz., the peripheral vascular collapse¹⁸ calls for additional treatment with phenylephrine (or related pressor substances).

In our patient, the hemorrhage was suc-

cessfully controlled by the administration of human fibrinogen. However, despite this and despite adequate blood transfusion, the shock state continued and only phenylephrine was effective in raising the blood pressure and maintaining it at a stable level.

Consequently, large doses of prophylactic antibiotics were given to prevent any complicating infection as is common in such cases (Table I).

Summary

A case of afibrinogenemia complicating spontaneous early abortion in the ninth week of pregnancy is presented. It is the first re-

port of this complication occurring so early in gestation.

The treatment of this condition is described. It includes (1) restoration of effective plasma fibrinogen levels, (2) correction of the shock state, and (3) prevention of subsequent infection.

Possible causative factors in the development of afibrinogenemia accompanying abortions are discussed.

We are very much indebted to Dr. E. Shafrir from the Department of Biochemistry of the Medical School for his kind help and advice.

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Fibrinogenolysis as a cause of obstetric hemorrhage

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THE multitude of observations^{6, 7, 25} concerning abnormal hemorrhagic states during pregnancy usually refers to the syndrome of afibrinogenemia or hypofibrinogenemia. The pathogenetic concept of a defibrinating syndrome²⁵ in which fibrinogen is consumed as the result of the autoextraction of thromboplastin has been substantiated by a variety of experimental observations, but the part which fibrinolysis plays in such cases remains open to discussion. This is partly because, in the cases observed to date, exact determinations of fibrinolytic activity have not been made. In only a few cases has blood been taken and investigated at frequent intervals in the acute phase. In addition, clinical determination of fibrinolysis is not yet satisfactory and particularly the so-called rapid methods (clot observation test and others)¹⁶ give no indication of any associated fibrinolytic activity.²³ Therefore, whether, and to what extent, fibrinolysis is a reactive process to the pathologic fibrin deposition or whether it is primarily of pathogenetic importance in hemorrhagic diathesis associated with pregnancy remains an open question.

Clinical and analytical findings, in a case of abnormal obstetric bleeding recently ob-

served by us, support our in vitro investigations^{8-10, 14} and warrant some discussion of the etiology and classification of obstetric hemorrhage.

In vitro investigations

In an exhaustive series of in vitro experiments,^{8-10, 14} we observed that when the balance between enzyme and inhibitor was altered, as under the influence of excessive plasmin activity, fibrinogen was inactivated. Fibrinogen lost its biologic activity, that is, its capacity to be converted by the action of thrombin into fibrin. But, as an in-coagulable globulin, "fibrinogen" was still present in considerable quantities (i.e., in concentrations exceeding the so-called critical value of 100 mg. per cent) when estimated by methods such as immune electrophoresis, paper electrophoresis, and precipitation by heat or ammonium sulfate. Particularly high plasmin activity was produced when a lyso-kinase, such as streptokinase (which acts by converting a proactivator into an activator) or an activator, such as urokinase, acted on plasminogen to form plasmin.

Thus, we were able to show that the incubation of an activator with fibrinogen resulted in the activation of plasminogen contained in the fibrinogen. This resulted, after a certain period of incubation, in a failure of the fibrinogen to clot in the presence of thrombin. We describe this process, in contrast to the earlier use of this term, as *fibrinogenolysis*, and define it as a process by

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which fibrinogen loses its biologic activity. A decrease in the fibrinogen concentration (hypofibrinogenemia), as has previously been assumed to occur, is not the only mechanism. It can be shown that the process which we call fibrinogenolysis results primarily in an inactivation of fibrinogen. As Alagille and Soulier¹ have already shown, other clotting factors may also have been affected, but according to our concept, these are reduced either during or after the process of fibrinogenolysis. We do not consider it correct to use the term "proteolysis" for this pathologic process, because in protein chemistry "proteolysis" is a term used to describe all kinds of nonspecific protein digestion. The term "pathologic fibrinolysis" is also difficult to justify because there is no agreement as to what should be described as physiologic fibrinolysis.

Clinical observations

We could demonstrate fibrinogenolysis as the cause of a hemorrhagic state in a patient, thus showing that this process can also occur in vivo leading to severe bleeding.

A cesarean section was performed for placenta previa. The patient had been subjected to an incompatible blood transfusion. As the result of this, when the cesarean section had been completed, the patient began to bleed and there was a complete breakdown of hemostasis. Coagulation was eventually restored and the bleeding controlled after the administration of protamine sulfate and ϵ -aminocaproic acid, 8 Gm. of fibrinogen, and 12 L of blood. The patient died later of acute emphysema.

The fibrinogen concentration did not fall below 150 mg. per cent, but the thrombin time was greatly prolonged, while the clotting time (value *r*), as measured with the thrombelastograph, was normal. A considerable activator-plasmin activity was found. Only after the infusion of fibrinogen could the presence of an inhibitor be demonstrated, and the thrombin time then became shorter, while the clotting time on the thrombelastogram became prolonged. The details of these results are to be published elsewhere.

Comment

We have seen a number of cases, which conform with those reported in the medical literature, of so-called "afibrinogenemia" in association with abruptio placentae, in which the fibrinogen level fell as low as 10 mg. per cent, leading to a true hypofibrinogenemia or afibrinogenemia.^{5, 22} There was a definite quantitative defect which could be justifiably explained by the concept of auto-extraction of tissue thromboplastin by a hydraulic pump mechanism.²⁵ But it was remarkable in these patients that clotting could be restored with less fibrinogen (1 or 2 Gm.) than was anticipated from the fibrinogen levels in the blood.²⁷

It is obvious that the quantitative relationships between fibrinogen levels and the degree of severity of the clinical picture have not yet been explained. In this respect, the method of fibrinogen estimation undoubtedly plays an important part. It would appear that there is a critical level below which blood becomes incoagulable. This level depends, however, on the method used for its estimation so that it is impossible to compare the results published by different workers. On the other hand, cases have been reported in which there was a definite hypofibrinogenemia in whole blood, but in which this did not lead to uterovaginal bleeding.^{4, 5, 15} It is possible to explain these observations by the presence of large amounts of fibrinogen contained within the retroplacental hematoma,²⁷ the latter acting as a fibrinogen collector of the organism. In this case, there would be sufficient fibrinogen available locally to control bleeding while in the general circulation there would be hypofibrinogenemia.

It has not gone unnoticed by careful observers, who have treated such patients, that the severity of the patient's condition is not entirely dependent on the fibrinogen level and that the response to treatment may be extremely variable, but no explanation of these discrepancies has been possible because the mechanism remains obscure.

The interpretation of some cases of afibrinogenemia is made particularly difficult

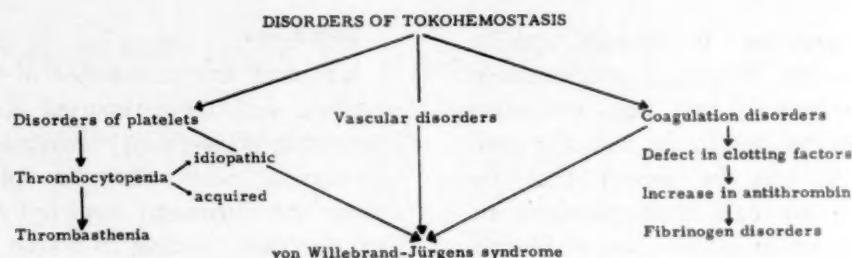


Fig. 1.

by the presence of lytic activity. This has usually been regarded as an accompaniment of shock and stress or as a reaction to the deposition of fibrin. Such an "associated" lytic activity,²² which can only be established through tests repeated at short intervals, might be regarded as a mechanism of self-protection of the organism. It is well known that afibrinogenemia or hypofibrinogenemia is preceded by a state of hypercoagulability^{7, 17, 22} in the course of which small clots are formed leading to microemboli, especially in the kidneys. It could be argued that if this phase of lysis did not occur the danger of a "crush-kidney" (lower nephron nephrosis) would be particularly great. The question is therefore raised as to whether any attempt should be made to prevent this lysis, as by the use of ϵ -aminocaproic acid. From the above discussion, the question formulates itself: What do we understand by pathologic and physiologic fibrinolysis? It seems certain, and is regarded as such by many authors, that this form of lysis, in association with thromboplastin intoxication, is not the primary cause of the loss of fibrinogen. Thus, Schneider brings up the question of whether or not plasmin may be prevented from attacking fibrinogen itself by the naturally occurring antiplasmin.²⁵

To "associated" fibrinolysis, we opposed "fibrinogenolysis" as a primary pathologic process. In such cases, the breakdown of the hemostasis is particularly striking. Fibrinogenolysis is more dangerous than defibrination because therapeutic control is more difficult than with cases of the Schneider syndrome. In this case, more fibrinogen is necessary than would be expected from the theoretical point of view.

The circumstances under which fibrinogenolysis is likely to occur are:

1. If the concentration of plasmin inhibitor falls. This has not yet been observed clinically with any certainty.

2. If, through the action of an activator, plasmin activity (activator-plasmin activity) is raised, then to a certain extent inhibitors are overpowered. This assumption is supported by the results of therapeutic fibrinolysis and thrombolysis.^{3, 24} The question remains open regarding the source from which the activators are derived in individual cases. In our case, we presume that as a result of the incompatible transfusion, activators were either formed in the blood or released into the circulation. The experiments of Deutsch¹³ with pyrogen injections have shown that such a mechanism is possible.

Intimately concerned in any discussion of fibrinogenolysis is the problem of inhibitory factors which to date have been considered in only a few cases; when present, they have been regarded to a certain extent as of independent pathogenetic significance. But in the light of recent facts revealed by research into fibrinogenolysis, this must be doubted. It is known that, with increasing plasmin activity, fibrinogen breakdown

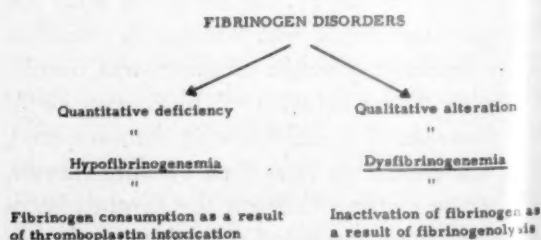


Fig. 2.

products are released which have an inhibitory effect on thrombin¹⁰⁻²¹ and blood thromboplastin.¹⁸ These substances decrease and disappear with further increase of plasmin activity or when lysis is complete. It is therefore unnecessary to assume that such an anticoagulant must be of a type like heparin, which as the result of shock might be released. It would seem much more likely, however, that fibrinogenolysis is associated with the activity of an anticoagulant that is released from fibrinogen, which would explain the reason for the appearance of the severe hemorrhagic states in these cases.

It is still not clear whether the so-called afibrinogenemia, which is sometimes associated with the retention of a macerated fetus in utero, is due to release of an activator or, as has previously been assumed, to the passage of nonspecific proteolytic enzymes from the macerated fetus into the maternal circulation.^{26, 28}

The argument that fibrinogenolysis results primarily in a pathologic state makes it necessary to contrast and distinguish a qualitative defect and a quantitative deficiency of fibrinogen. The alteration of other components of the clotting system, such as the thrombocytes, may not be discussed, it being without pathogenetic importance in this connection.

As already emphasized, with fibrinogenolysis it is not strictly correct to speak of

afibrinogenemia; therefore, in cases of obstetric coagulation disorders, the all-embracing term "disorders of tokohemostasis" would be preferable (Fig. 1). This term comprehends all cases of coagulation disorders in pregnancy, for instance, idiopathic thrombocytopenia. To designate the disturbances concerning fibrinogen, we would prefer the term "fibrinogenopathy," the latter to be subdivided into "afibrinogenemia and hypofibrinogenemia" on the one hand and "dysfibrinogenemia" on the other (Fig. 2). In the differential diagnosis of this condition, the important investigations, in addition to the estimation of lytic activity, would be the estimation of biologic activity by means of the thrombin time¹¹ and the total fibrinogen estimation.¹²

The discrepancy between thrombin time and the fibrinogen level has been confirmed by Sharp and associates,²³ who found a pathologic thrombin time in the presence of normal fibrinogen levels. We would suggest that, in these cases, they were dealing with the phenomenon of fibrinogenolysis, although the authors state (but without publishing their respective values) that no lytic activity was observed.

This new classification is not only of theoretic interest but also of therapeutic importance because these various types of coagulation defects have to be treated differently. The details will be discussed elsewhere.

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Intravascular defibrination in pregnancy with associated pituitary and kidney damage

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THE precise mechanism of postpartum hypopituitarism remains obscure, and it is uncertain whether the ischemic necrosis is initiated by embolic fibrin obstruction, general circulatory failure, or a combination of both. Postmortem study of patients dying soon after the development of the condition is necessary in order to elucidate this question. Patients who come to autopsy after years of clinical hypopituitarism will show grossly deficient pituitary substance, irrespective of the nature of the process which caused the destruction.

Sheehan⁸ established that pituitary necrosis is not an uncommon finding in women who die in the puerperium following hemorrhage and collapse during delivery. He noted that the necrosis, although found after hemorrhage and collapse at delivery, did not occur after hemorrhage and collapse in the absence of pregnancy. Sheehan postulated that the association with delivery is related to the change from the marked hypertrophy of the anterior pituitary during pregnancy to the rapid involution during the puerperium: "At a normal delivery there is physiological reduction of blood flow to the anterior lobe, and if in addition there is general circulatory collapse, then flow to the anterior pituitary is so reduced that thrombosis occurs in the vessels of the lobe, and leads to ischaemic necrosis." Sheehan also stated that the pituitary necrosis was not due to embolism as a result of puerperal

sepsis, as had previously been suggested. In the same paper Sheehan reported the finding of fibrin thrombi in several sinuses of the anterior lobe of a pituitary which had undergone extensive necrosis. The patient in this case had had eclampsia and an accidental hemorrhage and the terminal collapse was suggestive of amniotic fluid embolism.

McKay⁹ showed that intravascular deposition of fibrin was seen at autopsy in patients dying from eclampsia, bilateral renal cortical necrosis, and pituitary necrosis, and pointed out the possible relationship to the generalized Schwartzman phenomenon, and suggested that these complications of pregnancy had therefore a common etiology.

Weiner⁹ stated that bilateral cortical necrosis of the kidney was caused by a mechanism other than renal ischemia due to hypotension. Ober⁵ reported that of 7 patients who died with renal cortical necrosis 3 also had pituitary necrosis, and, in one, small fibrin emboli were seen within the pituitary sinusoids. All of these patients had accidental hemorrhages. Ober stated that cortical necrosis developed early in the course of accidental hemorrhage and not merely as a consequence of a hypotensive episode. However, Ober considered that the pathogenesis of cortical necrosis involved renal arteriosclerosis, and that the mechanism was prolonged intense renal vasospasm, with local formation of fibrin thrombi as a secondary phenomenon, due to anoxic damage to the vascular endothelium. He believed that all of the fibrin thrombi formed over a short span of time, and that once present coagula-

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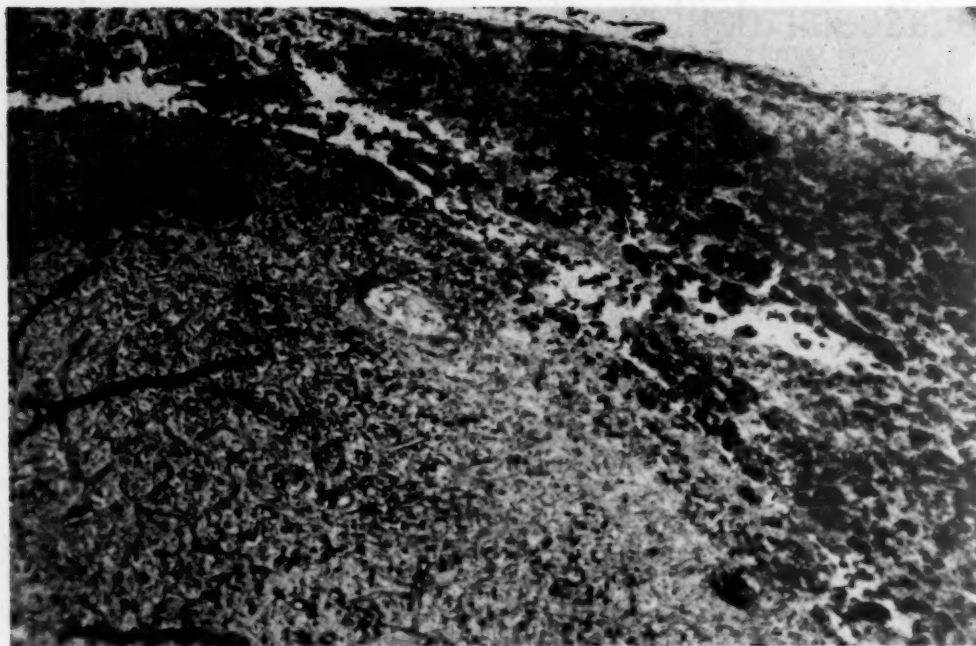


Fig. 1. Case 1. Anterior pituitary infarct with peripheral zone of surviving tissue. (Mallory PTH $\times 120$.)

tion necrosis of the renal cortex became inevitable. Anthone¹ stated that when hypofibrinogenemia complicates accidental hemorrhage, fibrin emboli may cause intravascular plugging of small kidney arterioles with resulting bilateral cortical necrosis.

McKay⁴ presented the autopsy findings in 7 patients who died as a result of septicemia and who showed intravascular fibrin thrombi associated with infarction of the renal and adrenal cortex and also of the anterior pituitary. One patient reported in his paper also had amniotic fluid embolism and hypofibrinogenemia.

Reisfield⁶ in discussing thrombotic thrombocytopenic purpura in pregnancy recorded the unexpected finding of hypofibrinogenemia in a patient who at autopsy showed fibrin thrombi in the kidneys, adrenals, and pancreas, and also an anterior pituitary infarct.

Schneider⁷ stated that intravascular defibrination produces intra-arteriolar circulatory obstruction especially in the pulmonary circulation, where the fibrin depositions may result in acute cor pulmonale. He added that these fibrin occlusions can disappear because of fibrinolytic activity.

The above review of the literature illustrates that intravascular fibrin deposition accompanies the necrosis seen in the pituitary and kidney during varied complications of pregnancy. However, opinions are divided as to whether the fibrin emboli are the precipitating factor causing ischemic necrosis or merely secondary associated findings.

Case reports

The following two case reports are further examples of different types of this defibrination syndrome.

Case 1. A multigravida, aged 34 years, had 8 living children. Two previous confinements had been complicated by mild antepartum hemorrhage. In the present pregnancy, induction of labor was attempted by intramuscular administration of Pituitrin when the patient was at 44 weeks' gestation. Abdominal pain developed 4 days later and was accompanied by moderately severe bright vaginal bleeding. Examination revealed a vertex presentation with the head high and mobile. Fetal movements were absent and the fetal heart inaudible. Vaginal examination revealed Type I placenta previa, and a lower uterine segment cesarean section was performed under ether anesthesia. The infant was stillborn and macerated. The patient

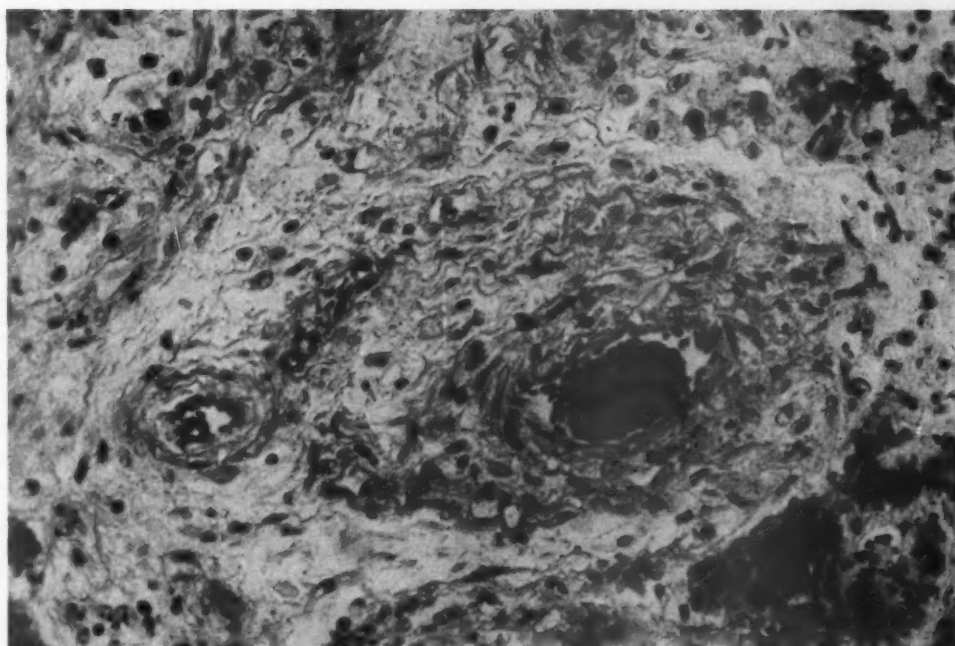


Fig. 2. Case 1. Fibrin embolus within arteriole at the junction of the necrotic and viable pituitary substance. (Mallory PTH. $\times 240$.)

was very shocked during and after operation and the blood pressure was almost unrecordable. During the 4 hours following operation 4 L. of blood was transfused. Because of continued bleeding, cutaneous bruising, and failure of extravasated blood to clot, hypofibrinogenemia was diagnosed, and 11 Gm. of fibrinogen was administered, with improvement of circulation and general condition. A sample of blood sent to the Royal Women's Hospital was found to contain 30 mg. per cent of fibrinogen. The patient's early postoperative course was marked by oliguria. Urinary output for the first day, 180 ml.; second day, 120 ml.; third day, 180 ml.; fourth day, 300 ml.; fifth day, 240 ml. with protein varying from 8 to 16 Gm. per liter. On the seventh postoperative day, the urinary output had risen to 410 ml. with 16 Gm. protein per liter, and by the tenth postoperative day to 1,980 ml. containing 4 Gm. protein per liter. The patient was given 1 liter of blood on the sixth postoperative day as the hemoglobin level was 7.5 Gm. per cent. On the ninth postoperative day the patient became mentally confused, and then died suddenly 10 days after cesarean section.

Autopsy findings. The kidneys were large and flabby with the cut surfaces revealing pale edematous cortex and congested hemorrhagic medullary pyramids.

The adrenals showed several small areas of cortical necrosis but were otherwise normal.

The pituitary contained extensive infarcts of classical appearance. Microscopic examination showed almost complete necrosis of the anterior pituitary, with only a small rim of surviving tissue around the periphery (Fig. 1). Small areas of hemorrhage were present in the necrotic areas. Intra-arterial fibrin emboli were demonstrated within the infarcted zone at the junction with the surviving tissue (Fig. 2). These emboli were few in number and were identified only by means of Mallory's phosphotungstic acid hematoxylin stain for fibrin. Fibrin emboli were not seen in similarly prepared sections from the other organs.

[**Final diagnoses.** Hypofibrinogenemia; anterior pituitary necrosis; bilateral renal cortical necrosis.

Comment. Accidental hemorrhage is the likely but unproved cause of the vaginal bleeding, abdominal pain, and fetal death in utero which occurred in this patient. Fibrinogen depletion explains the severe bleeding at operation which illustrated the danger of cesarean section without preliminary recognition and correction of a disordered clotting mechanism.

The demonstration of fibrin emboli within

the pituitary infarct suggests that its pathogenesis is related to intravascular defibrination resulting in arteriolar occlusion and ischemic necrosis.

The absence of fibrin emboli within other organs is understandable since the patient survived for 10 days after the defibrination episode, and the fibrinolytic enzyme system could dissolve such emboli in any area still possessing an intact circulation.

Case 2. A multigravida, aged 36 years, had a previous history of 7 normal confinements at term. The present pregnancy was uneventful until 34 weeks' gestation when there was a gradual onset of lower abdominal pain and tenderness over a period of 6 hours, and a loss of approximately 30 ml. of blood per vaginam. On admission the pulse rate was 104 per minute, blood pressure 120/70 mm. Hg, temperature 102° F., and the urine was free of protein. Neither generalized nor dependent edema was present. The uterus was enlarged to the size of a full-term pregnancy and was extremely tense and tender. The fetal heart beat was inaudible. Speculum examination revealed a normal cervix

with the internal os 2 cm. dilated and draining clear liquor. Clotting time was 4 minutes. Hemoglobin level was 9 Gm. per cent; blood Group B, Rh negative. Accidental hemorrhage was diagnosed. Morphine, 15 mg., was given, and crystalline penicillin, 0.5 mega unit, was ordered given every 6 hours, and sodium sulfacetamide (20 per cent solution) 1 Gm. every 6 hours. Blood was cross matched for transfusion. Three hours later the temperature was 103.6° F. and the pulse rate 140 per minute. The patient was vomiting, coughing and was slightly cyanosed. Proteinuria was noted for the first time. Sodium gardenal 180 mg. was given, and a transfusion commenced. Six hours after admission the patient's condition was considered satisfactory, when, with the second flask of blood running she collapsed suddenly, and developed extreme tachycardia and cyanosis. Moist sounds were audible at the lung bases. A further specimen of blood was withdrawn and, as this time no clot formed within 15 minutes, 5 Gm. of fibrinogen were administered by rapid intravenous injection. Ten minutes after the fibrinogen had been given the patient had a generalized convulsion and died.

Autopsy findings. Marked cyanosis of face and

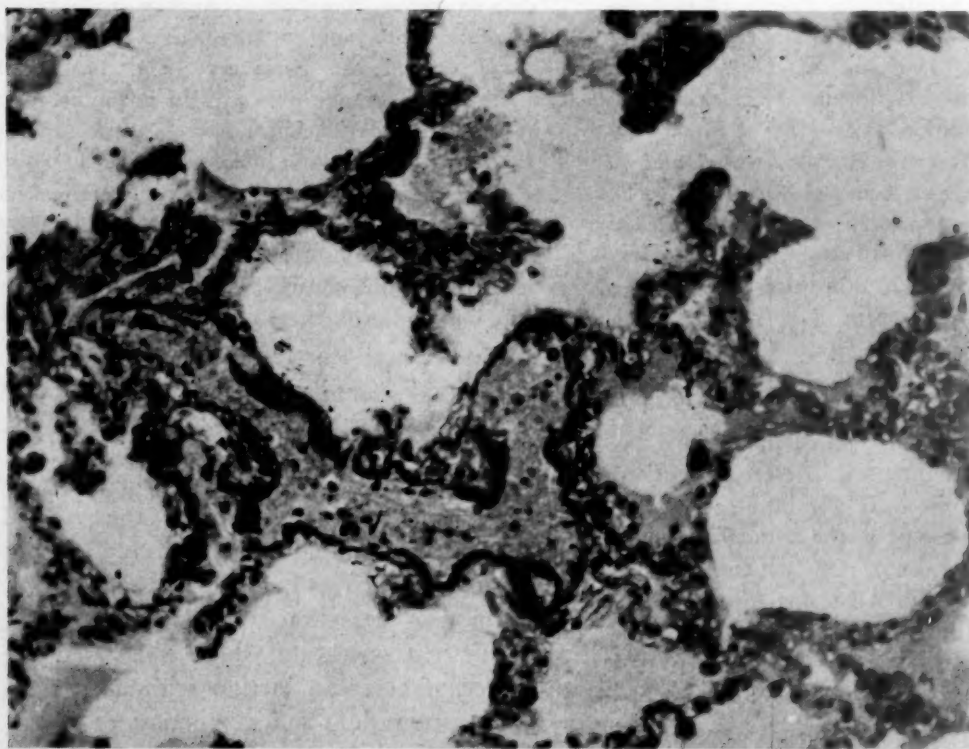


Fig. 3. Case 2. Lung showing alveoli and a pulmonary arteriole which contains many fibrin emboli. (Mallory PTH. $\times 120$.)

neck. At the first incision over the sternum there was a hissing escape of gas, and foam exuded from all small blood vessels. All blood was fluid. The kidneys were deeply congested. The liver was honeycombed with gas bubbles of all sizes. The uterine wall was thin, and the fetus was macerated. The placenta was attached to the uterine wall and there was no accidental hemorrhage.

MICROSCOPIC EXAMINATION. "Sections through the lungs showed, apart from patchy edema, no significant changes in the alveoli. However, many of the small vessels contained slimy material characteristic of amniotic fluid embolism. The kidneys showed no significant pathological features. Septic thrombi were seen in the vessels of the uterine wall." The above is an extract from the original microscopy report, but subsequent to this fresh sections were prepared and stained for fibrin by the Mallory technique. The lungs showed intra-arterial fibrin emboli which were present in abundance in every vessel examined (Fig. 3). The kidneys showed multiple fibrin emboli within every glomerulus examined (Fig. 4).

Cultures were taken from the uterine contents at autopsy, and the rare *Clostridium fallax* was

identified. Samples from the flasks of blood given to the patient revealed neither incompatibility nor bacterial growth when cultured.

Final diagnoses. Intrauterine *Clostridium* infection, massive intravascular fibrin embolization, hypofibrinogenemia.

Comment. In this patient the *Clostridium* septicemia seems to have initiated the defibrination process with the resultant clinical features of "amniotic fluid embolism" and hypofibrinogenemia. The patient showed all the features of the generalized Schwartzman phenomenon as described by McKay.⁴ McBride² also reported a maternal death due to *Clostridium* septicemia which followed a criminal abortion, and was associated with hypofibrinogenemia.

Unlike the patient described in Case 1, the patient in Case 2 died almost immediately after developing hypofibrinogenemia and it is therefore not surprising that the fibrin emboli were so numerous. Conversely, this patient did not survive long enough to develop histologic evidence of ischemic infarction in the organs involved by embolic

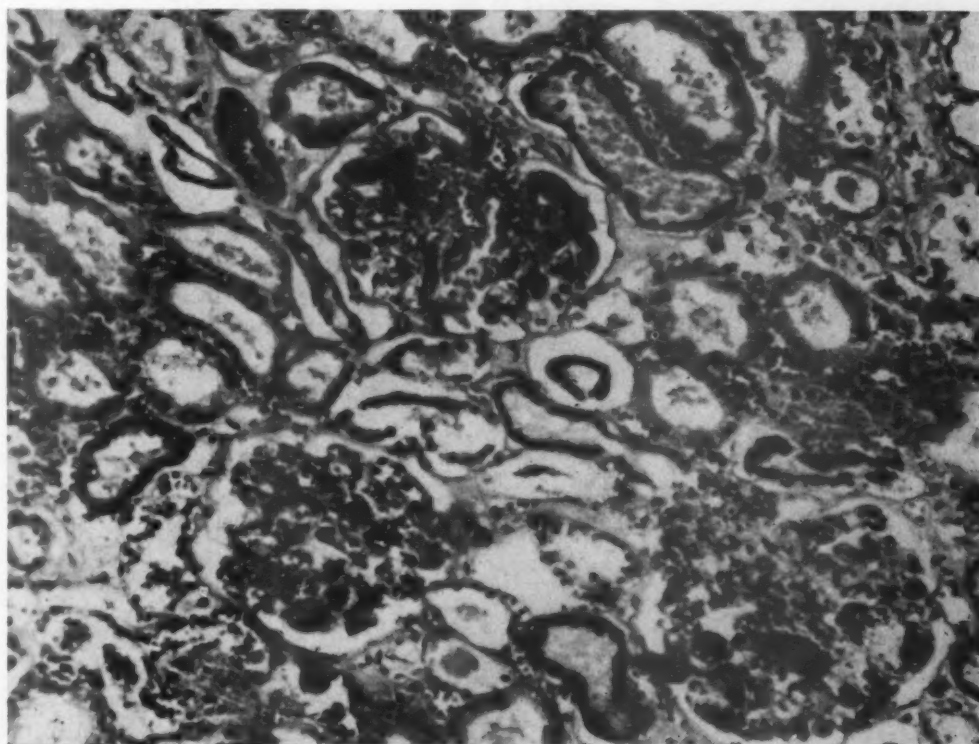


Fig. 4. Case 2. Kidney with many fibrin emboli within each glomerulus. (Mallory PTH. $\times 120$.)

fibrin occlusion; again in contradistinction to the patient described in Case 1. In most patients with hypofibrinogenemia the defibrinating agent is of placental origin and enters the uterine veins, and therefore fibrin emboli are mainly confined to the pulmonary circulation. However, in the generalized Schwartzman phenomenon due to septicemia, the defibrinating agent is widely disseminated throughout the systemic circulation. This also explains the numerous fibrin deposits seen in Case 2.

It is pertinent to consider whether intravenous administration of fibrinogen to such patients may cause acute cor pulmonale by initiating massive intravascular defibrination. This is a theoretical possibility should thrombin be present in the circulation. However,

although this patient died within 10 minutes of receiving fibrinogen, cyanosis and pulmonary crepitations were present prior to its administration. Also, complete absence of fibrinogen is unusual in patients with clinical hypofibrinogenemia, and therefore it may be assumed that all thromboplastin which has entered the maternal circulation has already been completely utilized in the defibrination process.

We wish to thank Professor Lance Townsend for helpful criticism and advice, and also to extend thanks to Dr. E. L. Vine, Mansfield, Victoria, and Dr. George Simpson, Royal Women's Hospital, for permission to quote Cases 1 and 2, respectively, and Miss M. L. Johnson for the photographs.

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Five years' experience with the chemotherapy of metastatic choriocarcinoma and related trophoblastic tumors in women

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EARLIER reports have described our initial observations in the treatment of metastatic choriocarcinoma and related trophoblastic tumors with the folic acid antagonist, amethopterin (Methotrexate—MTX).¹⁻³ We wish now to present our chemotherapeutic studies in 63 patients treated during the past 5 years, including those patients previously described. These patients initially received MTX. In addition, 13 were treated subsequently with several courses of vincalukoblastine (VLB), an oncolytic alkaloid derived from the plant, *Vinca rosea*.⁴⁻⁶

Materials and methods

Amethopterin was administered according to the intensive, intermittent regimen initially described by Li, Hertz, and Spencer.¹ This consisted of the daily intramuscular injection of from 10 to 30 mg. sodium MTX in aqueous solution at a concentration of 50 mg. per cubic centimeter. The usual course consisted of 5 consecutive daily injections but this was occasionally curtailed when early signs of marked toxicity supervened.

Vincalukoblastine sulfate was given intravenously each morning and each evening on each of 3 consecutive days in amounts

ranging from 3 to 6 mg. per dose. The freshly prepared saline solution was injected into the tubing of a rapidly running infusion of normal saline to minimize the local pain, thrombophlebitis, and local nerve damage seen in some cases.

Each course of either MTX or VLB was withheld until all toxicity from the preceding course had completely subsided.

Only patients who presented unequivocal radiological, hormonal, or clinical evidence of metastatic disease were admitted to this study. In 4 instances an elevated gonadotropic hormone titer persisting for several months after hysterectomy constituted the sole evidence of persistent trophoblastic disease. In all other cases metastatic disease was also manifested by lesions which could be demonstrated by physical or radiological examination.

The histological findings available to us either at the time of admission of the patient for study or during the time of chemotherapy are listed in Table I. Although subsequent findings indicated that several patients presented with diagnoses other than those found at autopsy, the initial diagnosis was retained for the present analysis. The criteria for pathological diagnosis are those of Novak.⁷

We have utilized the hormonal titer as a major guide in clinical evaluation and therapy. These titers are expressed as mouse

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Table I. Histological diagnosis on admission in 63 women with metastatic trophoblastic disease

Choriocarcinoma	44
Chorioadenoma destruens	10
Hydatid mole	5
Syncytial endometritis	1
Trophoblastic nodule	1
Decidual tissue	2

Table II. Findings on admission in 63 women with metastatic trophoblastic disease

Pulmonary metastases	52
Pelvic mass	19
Vaginal metastases	18
Intracranial metastases	6
Bowel metastases	3

Table III. Response to chemotherapy in 63 patients with metastatic trophoblastic disease (1955 to 1960)

	MTX	MTX plus VLB*	Total
No evidence of disease	28	2	30 (47.5%)
Persistent disease	2	5	7 (11.0%)
Dead after remission	16	6	22 (35.0%)
No response	4†	-	4 (6.5%)

*Thirteen MTX-resistant patients received VLB; 5 showed some regression of tumor and, in 2 of these, complete remission was obtained; the remaining 8 showed no response.

†Three died too early during the course of therapy to permit evaluation of response.

uterine units excreted per 24 hours. The determinations were made at least once weekly by a modification of the method of Klinefelter and associates.⁸ The urine specimens were quantitatively collected and were refrigerated continuously until processed. A urinary value of between 200 and 500 M.U. per 24 hours or less is normal in our laboratory for women who previously have had oophorectomies. In those patients in whom such normal urinary titers had been obtained, a further check for absence of chorionic gonadotropic hormone was made

in undiluted serum, according to a modification of the method of Delfs.⁹

In addition, because of the great frequency of pulmonary metastases, we have used frequent x-ray examinations to evaluate the patient's progress. Pelvic manifestations of disease, including uterine size, vaginal implants, uterine bleeding, and secondary obstructive effects on the urinary tract as revealed by intravenous pyelography, were also carefully followed. Central nervous system metastases were assessed by repeated neurological examinations, by serial electroencephalographic studies, and by scanning studies employing radioiodinated serum albumin as an indicator.

Because of anticipated toxicity, the patient's hepatic and renal status was determined by appropriate laboratory and clinical studies both before and at frequent intervals during chemotherapy. Also, because bone marrow depression was the most common and most serious form of toxicity encountered, the leukocyte, erythrocyte, platelet, and reticulocyte counts were determined at 1 to 3 day intervals.

All patients were treated in the hospital under constant medical and nursing care. Supportive therapy in the form of parenteral fluids, oral lavage with lidocaine, meticulous skin care in the event of toxic cutaneous manifestations, restriction to bed during episodes of profound leukopenia, and other general measures were rigorously employed in order to favor the patient's recovery from the frequently severe toxicity induced.

All surviving patients are available for follow-up and autopsies were performed on all but 3 of the patients who died. Follow-up during the first year consists of monthly

Table IV. Duration of 30 complete remissions*

4 to 5 years	3
3 to 4 years	3
2 to 3 years	7
1 to 2 years	13
½ to 1 year	4

*The term "complete remission" indicates total absence of evidence of residual disease by physical, radiological, and hormonal examination. (Compiled as of Oct. 31, 1960.)

visits and these are spaced at greater intervals in ensuing years.

The salient clinical features of these patients are listed in Table II. In general, this group of patients presented the picture of advancing disease despite the prior application of classical methods of management. Many had experienced extensive blood loss from hemorrhage from the uterus or vagina or less commonly the lungs or bowel. Numerous transfusions had been required in many cases, thus predisposing to the subsequent development of serum hepatitis.

Results and comment

Evidence of tumor suppression obtained in all but one of the patients who survived for a sufficiently long period to permit evaluation of the chemotherapy applied. Table III summarizes the results achieved as of the time of compilation of these data, Oct. 30, 1960.* It will be noted that 28 patients treated with MTX and 2 additional patients in whom MTX therapy had been supplemented with VLB now show no hormonal, radiological, or physical evidence of disease, a state we have termed "complete remission." The duration of these complete remissions is shown in Table IV. It should be emphasized that such remissions usually persist without further therapy once they are attained. However, since we have noted relapses in 3 other patients who appeared to have been in complete remission for 2, 3, and 12 months, respectively, we have preferred to apply the somewhat indecisive term "complete remission" to this type of usually sustained response, pending the further evaluation of the subsequent 5 year course in all of these patients. Nevertheless, the small number of relapses in patients previously presenting this pattern of complete and sustained response suggests that the tumor process has probably been eradicated in these 30 patients.

We have previously published figures illustrating radiological and hormonal evidence

*As of June 1, 1961, no patient reported with total remission has had a relapse (see Tables III and IV).

Table V. Duration of incomplete remissions in 29 women*

Duration	No. of cases
1 to 2 months	8
2 to 4 months	7
4 to 6 months	5
6 to 8 months	2
8 to 10 months	4
10 to 12 months	1
Over 12 months	2†

*Compiled as of Oct. 31, 1960.

†These remissions have lasted 29 and 43 months, respectively.

Table VI. Apparent primary cause of death in 23 autopsies

Cause	No. of cases
Intracranial hemorrhage	8
Intra-abdominal hemorrhage	5
Pulmonary hemorrhage	1
Respiratory insufficiency	4
Septicemia	5*

*Related in 4 cases to MTX toxicity.

Table VII. Relationship of age to therapeutic response in 63 patients*

Response	Mean range (years)	No. of cases
Complete remission	26.9	30
Incomplete remission	26.4	7
Dead	28.8	26

*The 63 patients ranged in age from 15 to 51 years with a mean of 27.7 years.

of regression of extensive metastatic pulmonary disease.³ Such manifestations are also shown in Figs. 1 and 2.

Fig. 3 indicates the number of courses of MTX required to induce complete remission in the 28 patients responding to MTX alone. From 1 to 11 courses were required, with a high frequency of complete remissions being induced by 3 to 5 courses. Those receiving only 1 or 2 courses showed prolonged toxicity, thus necessitating a prolonged delay in therapy during which complete remission intervened.

A less complete but unequivocal therapeutic response was seen in 29 patients. These 29 patients failed to show a return to a normal gonadotropin level but exhibited vary-

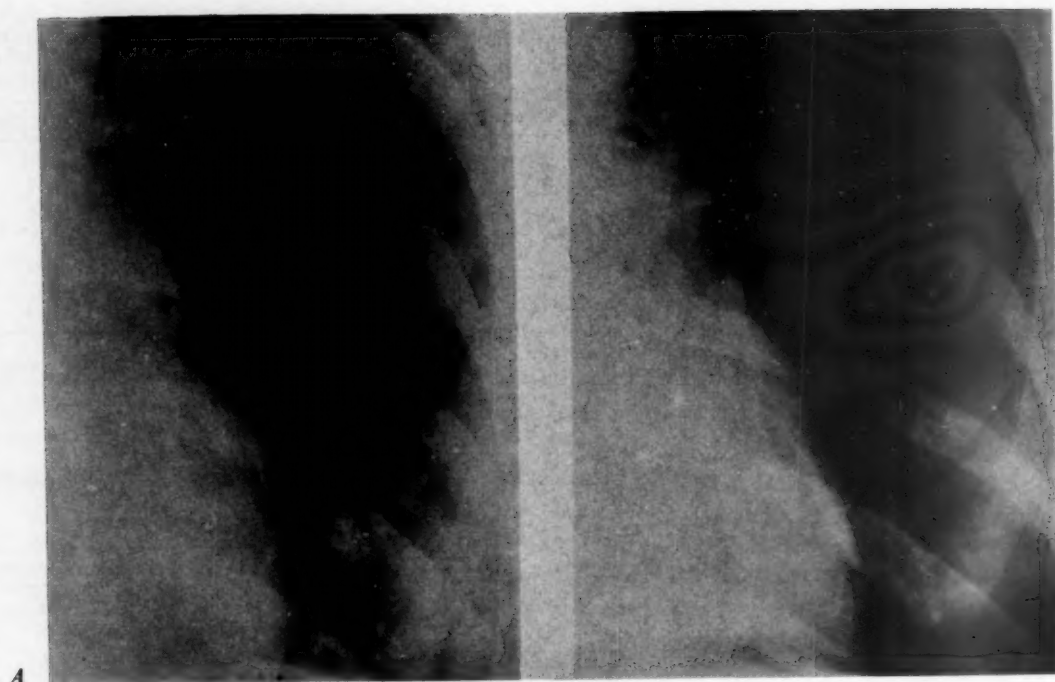
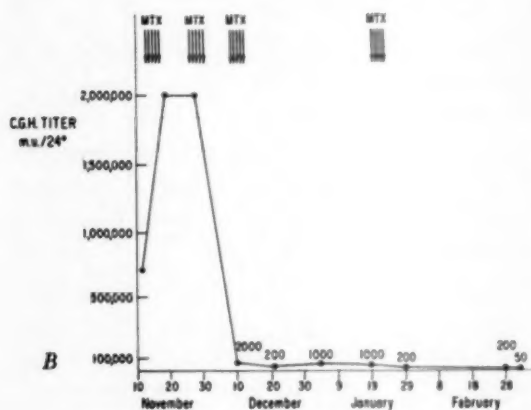


Fig. 1. X-rays (A) and gonadotropin titer (B) in patient with choriocarcinoma in complete remission since February, 1960. Vertical arrows indicate 5 day courses of amethopterin.



ing degrees of response characterized by x-ray and physical evidence of tumor regression, substantial decrements in hormone titer, cessation of vaginal, pulmonary, or gastrointestinal bleeding, correction of neurological abnormalities, and general physical rehabilitation. Only one patient failed to show any response, and the remaining 3 women died too soon after the start of therapy to permit evaluation.

Table V lists the duration of such incomplete remissions. The duration of an incomplete remission is determined by the interval between a substantial drop in titer and its subsequent re-elevation. It will be seen that

in some instances these periods of remission were quite prolonged. However, these patients ultimately exhibited total resistance to further therapy with MTX as well as to subsequent therapy with VLB. In 22 patients the disease was then reactivated, and they died of various manifestations of disease as listed in Table VI. Hemorrhage is the most frequent lethal mechanism in such cases. Seven of these patients with an incomplete remission are alive and undergoing further therapy.

We have attempted to determine what factors may affect the degree of therapeutic response obtained in any given case. Table

VII presents the relationship between age and therapeutic response. It is obvious that this is not a significant factor.

The histopathological features are widely considered to have a decisive influence upon the ultimate prognosis in any given case.^{7, 10, 11} Whereas these considerations are tenable when one includes all cases from their incipency, this factor seems not to be equally applicable to the problem of the response to chemotherapy in such advanced cases as the present series represents. This conclusion is based on a review of the data in Table VIII which indicate a remarkably comparable survivorship in those patients presenting a histological diagnosis of choriocarcinoma and in those presenting on admission other diagnoses such as chorioadenoma destruens or other less ominous histological features. Perhaps, the vagaries of histological diagnosis in this complex spectrum of trophoblastic tumors described by Park¹⁰ help to rationalize the observed variability in clinical pattern. Nevertheless, our experience with the most advanced phases of the clinical course of patients with metastatic trophoblastic disease leads us to place little prognostic reliance on the prior histopathological diagnosis in such cases.

The role of prior operation in determining the type of response to chemotherapy is summarized in Tables IX and X. Hysterectomy had been carried out in 41 of our patients prior to chemotherapy. The per-

centage of complete remissions is 47 per cent in this group and 50 per cent in the patients who had not had a hysterectomy. Thus, the presence or absence of the uterus appeared to play no significant role. Moreover, the 9 premenopausal patients who had not had a hysterectomy and who are in complete remission have resumed normal menses and 2 have since experienced a normal, full-term pregnancy. The 2 additional patients who had not had a hysterectomy and who are in complete remission were postmenopausal.

With respect to ovariectomy, however, there appears to be a substantially more favorable result in the ovariectomized patient. The numbers in these respective groups are, however, quite small, and, although a statistically significant difference is observed, the data must be regarded as simply suggestive of the desirability of doing an ovariectomy whenever a hysterectomy is undertaken.

Perhaps the most critical factor in the response to chemotherapy appears to be the duration of the disease process prior to the onset of treatment. Table XI shows that 18 of 25 patients treated within 4 months of the onset of the disease experienced a complete remission. In contrast, only 7 of 27 patients treated later than 6 months after the onset of disease showed such a favorable outcome. Hence, every effort must be directed toward earlier diagnosis and therapy in women with trophoblastic disease.

Table VIII. Relationship of histopathology to chemotherapeutic response in 63 patients*

	No. of patients	Complete remission	Incomplete remission	Dead
Choriocarcinoma	44	21 (48%)	4 (9%)	19 (43%)
Destruens, etc.	19	9 (47%)	3 (16%)	7 (37%)
All cases	63	30 (48%)	7 (11%)	26 (41%)

*For difference in response between choriocarcinoma and others, $p = > 0.95$.

Table IX. Effect of prior hysterectomy upon chemotherapeutic response*

Hysterectomy	No.	Complete remission	Incomplete remission	Dead
No	22	11 (50%)	2 (9%)	9 (41%)
Yes	41	19 (47%)	5 (12%)	17 (41%)

*For difference between patients with and without prior hysterectomy $p = > 0.95$.

Numerous observers have concluded that choriocarcinoma following a term pregnancy carries a more grave prognosis than does that following a hydatid mole or abortion.^{10, 15} Table XII summarizes our findings in this regard. These results support the conclusion that this factor has little effect on the outcome of therapy in cases with established, metastatic disease.

It might have been anticipated that those patients with a limited extent of disease as reflected by relatively small elevations in titer as well as by minimal clinical and x-ray findings would have a better prognosis. From the data in Table XIII there appears to be no correlation between the height of the initial titers with the response to therapy. We have observed complete remissions in some patients with very high titers and only limited response to therapy in others with little evidence of disease.

The specific metastatic site is considered to play a determining role in the outcome of trophoblastic disease.^{7, 10, 11} Thus, brain metastases as well as pulmonary metastases are considered especially lethal, whereas vaginal implants appear to be more prone to regression. In this series (Table XIV) metastasis to the brain failed to yield definitively to chemotherapy in 5 of 6 cases. However, the patients with pulmonary metastases fared almost as well as did all the patients taken as a group. The relatively poor outcome in patients with pelvic masses was in part attributable to lower urinary tract obstruction in 2 cases, necessitating a nephrostomy and attended by unusually severe MTX toxicity. An additional patient in this group died of local invasion and hemorrhage.

The major toxicity induced in patients treated with such intensive regimens of either

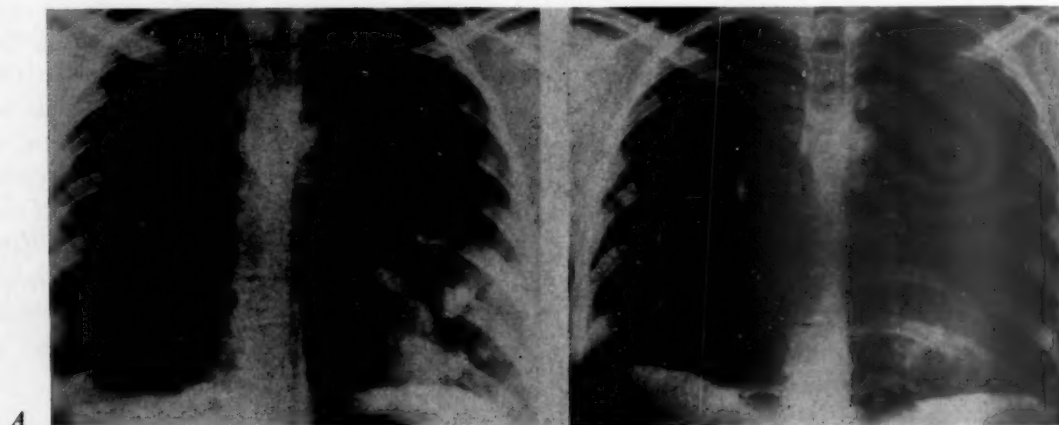


Fig. 2. X-rays (A) and gonadotropin titer (B) in patient with choriocarcinoma in incomplete remission since March, 1961, following 6 courses of amethopterin.

Table X. Effect of prior ovariectomy upon chemotherapeutic response*

<i>Ovariectomy</i>	<i>No.</i>	<i>Complete remission</i>	<i>Incomplete remission</i>	<i>Dead</i>
No	13	3 (23%)	2 (15%)	8 (62%)
Yes	28	16 (57%)	3 (11%)	9 (32%)

*For difference between ovariectomized and nonovariectomized patients, $p = > 0.05$.

Table XI. Effect of duration of disease before chemotherapy upon response*

<i>Duration</i>	<i>No.</i>	<i>Complete remission</i>	<i>Incomplete remission</i>	<i>Dead</i>
2 months	7	6	-	1
2-4 months	18	12	1	5
4-6 months	11	5	2	4
6-12 months	13	4	2	7
Over 1 year	14	3	2	9

*For difference between duration of less than 4 months and more than 4 months, $p = < 0.01$.

MTX or VLB constitutes a substantial hazard to the patient and a distinct challenge to the responsible physicians and nurses. One death was clearly attributable to MTX toxicity. In 4 additional cases MTX toxicity appeared to play a contributory role in the death of the patient since MTX was given in full dosage to patients with prior hepatic damage or impaired renal or bone marrow function. In these cases the terminal clinical state was characterized by overwhelming septicemia, granulocytopenia, thrombocytopenia, and varying degrees of hepatic decompensation. We have since learned that these findings constitute indications for either withholding the drug or substantially reducing the dosage. Bearing these precautions in mind, we have not encountered irreversible toxicity from MTX since the admission of the twenty-fourth patient in this series of 63 cases.

We must therefore emphasize that such rigorous chemotherapeutic efforts are contraindicated in patients showing prior hepatic, renal, or bone-marrow damage. Moreover, intensive medical and nursing care is essential to the recovery of the patient from the induced toxicity.

The major features of MTX and VLB toxicity have been previously detailed.^{3, 6} Additional guidance in regulating MTX

therapy may be obtained from Table XV, which shows our experience with respect to the necessary intervals between courses. It will be noted that initially 68 per cent of patients required only 10 days for recovery, whereas only 55 per cent recovered in so short a time after the third course.

In considering the distinctive toxicity of VLB, its neurotoxicity and marrow depressant effects are to be emphasized (Table XVI).⁶ The profound and selective reduction in the polymorphonuclear leukocyte count predisposes to systemic infection. Specific evidence of infection or in some cases severe febrile reactions when associated

Table XII. Apparent type of pregnancy immediately preceding onset of trophoblastic disease

<i>Type of pregnancy</i>	<i>No. of cases</i>	<i>Complete remission</i>	<i>Incomplete remission</i>	<i>Dead</i>
Full term delivery	15	7	1	7
Hydatid mole	29	13	3	13
Abortion	19	10	3	6

Table XIII. Effect of initial titer on response to chemotherapy

<i>Titer*</i>	<i>No. of cases</i>	<i>Complete remission</i>	<i>Incomplete remission</i>	<i>Dead</i>
Below 20,000	5	2	1	2
20,000 to 50,000	4	2	1	1
50,000 to 100,000	6	4	1	1
100,000 to 500,000	12	7	-	5
500,000 to 1,000,000	5	4	-	1
Above 1,000,000	31	11	4	16

*Expressed in mouse uterine units per 24 hours.

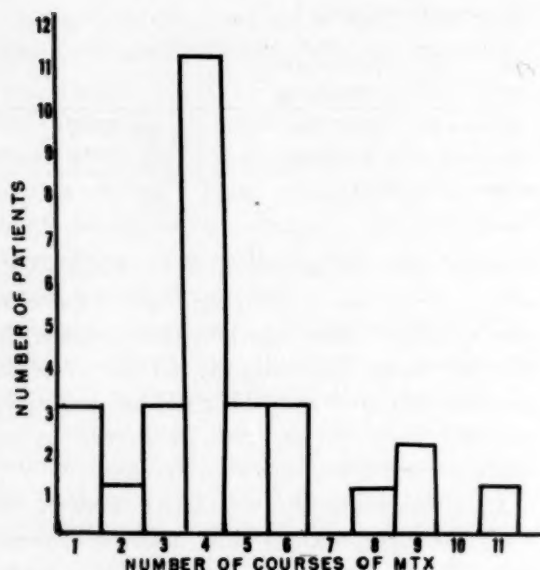


Fig. 3. Number of courses of amethopterin required to induce complete remission in 28 patients.

with marked granulocytopenia have been regarded as indications for antibiotic therapy. In addition, we have used reverse isolation when such patients exhibit signs of impending or actual systemic infection associated with profound leukopenia. We have had no instance of irreversible toxicity with VLB under these conditions.

The ready reproducibility of quantitatively assessable responses in a fairly constant time relationship to specific chemotherapy in 59 of 63 cases of metastatic trophoblastic disease leaves no doubt as to the efficacy and value of the therapy applied. However, the full evaluation of the over-all therapeutic accomplishment with these forms of chemotherapy is complicated by deficiencies in our knowledge of the natural history of this type of disease. Also, the potential role of such

accessory therapy as transfusions, antibiotics, and emergency surgical procedures to control massive hemorrhage must be considered. Thus, comparison with series in the literature from periods antedating the availability of such aids is inappropriate. Moreover, the reporting of the sporadically favorable outcome of a single case has provided little basis for evaluating the frequency of such events. Park¹⁰ has emphasized the frequency with which even expert pathologists will disagree in their diagnosis of a given lesion. Nevertheless, the precise morphology is widely considered to play a vital role in the ultimate outcome. Also, many series fail to show what proportion of the patients had metastases at the time of the primary operation. The duration of follow-up is seldom stated but in most instances it does not exceed 1 or 2 years.

The literature therefore provides little basis for truly adequate comparison with the present series. However, two substantial series of cases of metastatic choriocarcinoma which may be considered somewhat comparable with our 44 cases with a clear diagnosis of metastatic choriocarcinoma are available for comparison. Thus, Park¹¹ reported that of 158 patients with choriocarcinoma and pulmonary metastases only 3 were known to have survived. Moreover, Park could identify in the world literature only 20 cases of choriocarcinoma with pulmonary metastases which were known to have regressed.¹¹ Also, Brewer reported only 6 five-year survivals among 103 patients with metastatic choriocarcinoma recorded in the Mathieu Registry.¹²

Although such data provide only a crude gauge for the estimation of the degree of

Table XIV. Effect of metastatic site on response to therapy

Site	No. of cases	Complete remission	Incomplete remission	Dead
Pulmonary metastases	52	22 (42%)	6 (12%)	24 (46%)
Pelvic mass	19	6 (33%)	3 (15%)	10 (52%)
Vaginal metastases	18	10 (56%)	2 (11%)	6 (33%)
CNS metastases	6	1 (17%)		5 (83%)
GI tract	3	1 (33%)		2 (67%)
Other	9	3 (33%)		6 (67%)

effectiveness of the therapy employed by us in patients with metastases, it may be imputed that prolonged survivorship in patients with metastatic choriocarcinoma has probably been raised in our series from about 6 to 48 per cent.

As for chorioadenoma destruens and related lesions, estimates of a 50 per cent survivorship of undetermined duration in patients with pulmonary metastatic disease are drawn from several series.¹³ However, even metastatic disease at other sites results in a mortality of 20 to 30 per cent.¹⁰ Thus a survivorship of 48 per cent in our series of distinctly advanced cases may or may not reflect an increased over-all survivorship in this presumably less lethal form of metastatic trophoblastic disease. Nevertheless, the regularity with which major regressions followed chemotherapy establish the usefulness of such treatment even in cases in which the histological findings may imply a greater probability of a favorable outcome.

This interpretation is further supported by the fact that of 6 patients in our series with such relatively favorable histological diagnoses, 4 were found to have extensively metastasizing choriocarcinoma at autopsy, one still had chorioadenoma destruens, and the remaining patient died of MTX toxicity with no apparently viable trophoblastic cells being found. In contrast, however, in not one instance among 17 cases was a prior diagnosis of choriocarcinoma altered by the autopsy findings. Hence, it is clear that the prior histological findings in any given case are applicable to the state of the disease at the time the tissue is obtained and they may have little pertinence to the subsequent findings as the clinical course evolves.

Because of the numerous variables involved in diagnosis and evaluation of these several series, a more precise comparative statistical analysis of our data would be of little significance. We may, however, conclude that the chemotherapy applied in our cases has been of substantial value but that this can be quantitatively expressed in only very approximate terms. Meanwhile, a detailed epidemiological study including a cor-

Table XV. Time interval required for recovery from toxicity from MTX*

Course	10 days	10 to 15 days	Over 15 days
First	68%	11%	21%
Second	58%	21%	21%
Third	55%	18%	27%

*Calculations are based on a total of 350 courses.

Table XVI. Manifestations of toxicity in 16 cases treated with VLB*

Effect	No. of cases
Marrow suppression	16
Constipation	15
Malaise	15
Generalized aching	15
Parotid pain	14
Loss of reflexes	14
Mental depression	12
Abdominal cramps	12
Paresthesias	10
Infection	8
Alopecia	9
Bladder dysfunction	7
Transient phlebitis	6
Local neuropathy	4
Fever alone	4
Tachycardia	2

*These include 11 female and 5 male patients.

relation of histology and prolonged follow-up of patients treated by modern methods other than chemotherapy is needed in order to provide a more firm basis for such quantitative evaluation. It would, however, seem ethically as well as clinically unfeasible to undertake a double-blind evaluation at this time in view of the unquestionably favorable effects obtained by us and by others¹⁴ with these forms of chemotherapy.

The distinctly differing mechanisms involved in the oncolytic effects of MTX and VLB are apparent in MTX-resistant cases. In addition, the inherent capacity of the host to resist and in some cases to throw off this usually highly invasive type of tumor is considered by some to arise from a genetically determined incompatibility between fetal tissue and the internal environment of the maternal host. In this light, chemotherapy may simply augment or facilitate this factor of resistance,

Further exploration of the potential usefulness of additional oncolytic agents should be stimulated by the substantial and yet limited therapeutic effects reported at this time.

Summary

In 63 women with metastatic trophoblastic disease, intensive chemotherapy with the folic acid antagonist amethopterin supplemented in some by vincalukoblastine, an oncolytic plant alkaloid, has led to complete remission in 30 patients who have been free of hormonal, radiological, or physical evidence of residual disease for from 6 months to 5 years. Seven patients now in incomplete remission continue on treatment. In addition, of the 26 patients who have died, 22 had obtained substantial but incomplete remission. Such remissions were characterized by marked suppression of tumor, in many instances

leaving a persistently elevated hormone titer as the only evidence of persistent disease. Such incomplete remissions have lasted from 1 month to more than 43 months.

The hazards of toxicity attendant upon this intensive form of chemotherapy may be largely obviated by proper case selection, by less intensive therapy in patients with liver or renal impairment, and by adequate supportive medical and nursing care, thus rendering the risk involved clinically acceptable.

The highly variable clinical course of choriocarcinoma and related trophoblastic disease, with its indeterminate frequency of spontaneous regression, renders an exact appraisal of therapeutic accomplishment very difficult. However, the present data clearly establish the substantial therapeutic value of intensive chemotherapy in women with metastatic tumors of trophoblastic origin.

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Amethopterin in the treatment of trophoblastic tumors

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DURING the 10 year period of 1947 to 1956, 21 women dying of choriocarcinoma were autopsied in the Department of Pathology of the University of the Philippines and Philippine General Hospital Medical Center. These 21 choriocarcinoma deaths represented 10 per cent of the total malignant tumors found in women in the autopsy material of this department. Since 1956, 10 other cases have come to autopsy. So gloomy was the outlook of choriocarcinoma that we dreaded seeing any case, for once the diagnosis was made it was tantamount to pronouncing a death sentence on the patient. During the past 12 years, excluding the few reported in the present series, we have not seen a case of metastatic choriocarcinoma where the patient survived.

Background

In 1953 Li,¹ working at the Sloan Kettering Institute and at the Memorial and James Ewing Hospitals, gave the antifolic drug amethopterin to a young hypophysectomized woman afflicted with metastatic malignant melanoma. As part of the study, urinary chorionic gonadotropin assay was done bi-weekly and was found to be positive. A slow

decline of the titer was noticed after amethopterin therapy was started, and when the study was completed the urinary gonadotropin was absent. This incidental laboratory finding led to speculation as to its possible value in the treatment of chorionic gonadotropin-producing tumors. Li and Hertz² and subsequently Hertz and associates³ reported on the use of the folic acid antagonist amethopterin in choriocarcinoma and chorioadenoma destruens. The rationale for this arose from separate laboratory and clinical observations suggesting a high folic acid requirement during pregnancy.

Nelson and Evans⁴ demonstrated the high fetal need for folic acid in the rat. Thiersch,⁵ as a matter of fact, brought about abortion in women by giving them sodium aminopteroylglutamate and had shown that, in the rat or in the monkey deficient in folic acid, the uterus is incapable of growth in response to administered estrogen.

Hertz reasoned that choriocarcinoma and related trophoblastic growths originating as they do in the fetal chorion and initially involving the uterus might be adversely affected by folic acid antagonists. Amethopterin was accordingly given orally or intramuscularly in doses of 10 to 30 mg. in consecutive 5-day courses.

In the series of Hertz, partial remission was seen in 7 of the 27 cases. However, a striking drop in titer was seen in all, and pulmonary metastases in 3 completely dis-

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appeared. Transient remission was seen in 10 cases. Six patients died after initial response and one patient died from drug toxicity. The over-all mortality so far is 22 per cent.

Of these 27 cases in the Hertz series, 19 were unequivocally choriocarcinoma. There were 5 cures which constitute 26.5 per cent of the group. When one considers that the cases so treated were those with metastases, the figure 26.5 represents a significant achievement.

Program of treatment

Hertz and associates arrived at a regimen designed to give intensive intermittent therapy. Judged by ordinary doses of the folic acid antagonist for patients with acute leukemia, the method of administration was heroic. Based on the studies of Golden measuring the therapeutic effect in mouse leukemia and of Condit measuring the conversion of folic acid to folinic acid in man, the daily oral dose of Hertz was five to ten times the average adult dose used in acute leukemia. Folinic acid is necessary in the synthesis of the purine and pyrimidine bases which are components of the DNA of the chromosomes and the RNA of the cell cytoplasm. With antifolic drugs, mitosis and cell reproduction are slowed down. Acquired drug resistance is the bugbear in chemotherapy, and, in Hertz' cases, 17 patients probably had acquired drug resistance—certainly 10 out of these 17 had definite drug resistance. Additional therapy proved ineffective.

We, therefore, proposed to carry out our study of the chemotherapy of trophoblastic tumors along the following lines:

1. Administer intensive therapy in doses of 15 to 30 mg. daily over longer continued periods of time instead of intermittently at 5 day intervals.
2. Treat choriocarcinoma by hysterectomy and bilateral salpingo-oophorectomy whenever possible and institute chemotherapy soon after operation, usually on the second postoperative day.
3. Repeat chemotherapy in the same man-

ner when most of the signs of toxicity have disappeared but before all the signs have disappeared. Skin lesions and the falling of hair, for instance, take a long time before cure. The almost complete disappearance of stomatitis and the ability of the patient to begin to eat and swallow comfortably marked the point when treatment was usually resumed.

4. Treat chorioadenoma with or without metastases with amethopterin alone in the younger patient where saving the uterus and the childbearing function is important. The young woman who, following expulsion of a hydatidiform mole and subsequent curettage, continues to have an enlarged uterus, persistent bleeding without evidence of metastases, and a positive chorionic gonadotropin test, has always presented a problem. We proposed to treat such patients with antifolic therapy and not with hysterectomy.

5. Treat all cases of hydatidiform mole by curettage and follow this in alternate cases with amethopterin therapy in an effort to evaluate its effect in successfully preventing choriocarcinoma. The results of this study will be reported later.

Case material

Our experience is admittedly limited and recent. A summary of our cases follows: Seventeen cases of trophoblastic tumors were treated during the past 3 years. Twelve were unequivocally choriocarcinoma. Three were undoubtedly cases of chorioadenoma with metastases and one was a case of probable chorioadenoma where curettage was carried out twice after expulsion of molar cysts, where uterine bleeding continued, and where a persistent and rising titer prompted us to institute amethopterin treatment. A hysterectomy was not done. The chorionic gonadotropin level promptly became normal and the patient subsequently had normal menstruation periods with a secretory phase endometrium. The seventeenth case was also a choriocarcinoma but was atypical even in this clinical entity where atypicality is the rule.

The 3 cases of chorioadenoma with metastases are broken down into:

1. A case with vaginal and paraurethral metastases. A biopsy specimen of the metastatic nodule was obtained but the metastases were not removed. She was given 117.5 mg. of amethopterin. The vaginal and paraurethral lesions disappeared. The gonadotropin level dropped from 1:64 to 0. Hysterectomy was not carried out.

2. A case of chorioadenoma with pelvic mass. The chorionic gonadotropin level was 1:16. Hysterectomy was carried out but the pelvic mass could not be safely removed. The patient received 235 mg. of amethopterin in divided doses. The hypogastric mass disappeared after a 2 month period and the hormone level went down to 0.

3. A case of chorioadenoma destruens with metastases to the lungs. Biopsy of a lung lesion revealed trophoblasts and hemorrhagic necrosis. The patient was given three courses of amethopterin totaling 320 mg. The chest lesions disappeared and the chorionic gonadotropin level became negative.

In all the 3 cases, the chorionic gonadotropin level dropped to 0 and remained there. These patients, who have been normal clinically, radiologically, and hormonally for a period of over 2 years may be considered cured.

Twelve patients with choriocarcinoma have been treated (Table I). Nine of these when first seen were critically ill, were emaciated, and had a great deal of respiratory distress. All but one had a hysterectomy and bilateral oophorectomy either in our service or before admission to our service.

Results

Of these 12, 5 patients with lung metastases and positive chorionic gonadotropin were treated with amethopterin in doses of 330 to 447.5 mg. and have shown complete remission over a period of 3 years. The lung lesions disappeared usually over an average period of 3 months and the gonadotropin level has been consistently negative in the urine and in the serum. The patients

Table I

Total number	12	
Cures (3 year salvage)	5	41%
Partial remission		
Probably cured	2	
Remission but not cured	1	
Partial remission helped by lobectomy	1	33%
Deaths		
Drug failure	1	
Drug toxicity	2	25%

have gained weight and physically, hormonally, and radiologically are, during a 3 year period, apparently cured. They represent a 3 year salvage of 41 per cent of all choriocarcinomas.

Four patients showed a great deal of improvement with amethopterin. Two, we believe, are cured but the lung lesions, although almost gone, may still be seen. Hormonally, they have been consistently normal. These 2 patients, like the first 5, were in critical condition on admission, emaciated, toxic, and dyspneic. While it is still too early to tell, as they have been under observation for only a year, we are of the feeling that the lung lesions are no longer active and may represent fibrosis and organization.

One patient with bilateral pulmonary metastases developed drug resistance. The lung lesions have diminished in size but the chorionic gonadotropin is occasionally positive until treatment is reinstituted, when it becomes negative, only to reappear after medication is stopped. She has received a total of 880 mg. given in 13 courses.

The fourth patient in this group of incomplete cures was one we saw first because of probable missed abortion. She was 10 weeks amenorrheic and bleeding. The pregnancy test was weakly positive. The uterus, however, was normal and nonpregnant in size. Curettage revealed only proliferative endometrium. Because of the finding, a chest plate was taken and three large lesions were found in the left lung. A hysterectomy was not done since the patient was young and had no children and we were in the stage of this investigation where we felt amethopterin

would effect a cure in almost all cases. The lung lesion regressed, and the chorionic gonadotropin was absent for 6 months, only to become positive again. During this time, she had irregular menstruation periods from a proliferative endometrium. The lung lesions seemed somewhat larger. A lobectomy was carried out and the lesions showed choriocarcinoma which in one area was almost perforating the bronchus. The chorionic gonadotropin promptly disappeared after the lobectomy and has been consistently absent. She has had regular menstruation periods and the endometrium has shown good secretory reaction.

There were 3 deaths. Two patients died during the first course of therapy because of drug toxicity. One of the patients had extensive liver damage from schistosomiasis and the other patient, who had undergone a hysterectomy in another hospital, had a hydronephrosis secondary to a ligated ureter. The left kidney had a nephrolithiasis. We believe that the drug toxicity was worsened by the poor liver and renal function in these 2 patients.

The seventeenth case of trophoblastic tumor is a case which we feel is atypical and unusual. This turned out to be the third death in our series. The patient had had a hysterectomy for chorioadenoma destruens. She also had lung lesions, one of which was removed for histological study and showed choriocarcinoma. This case, however, was unusual in that a positive chorionic gonadotropin test was never obtained in the serum or in the urine. The patient was treated with amethopterin, and, since the lesion showed no regression, cobalt therapy was instituted. Liquefaction and regression of the lung lesion followed radiation therapy, but the patient soon developed cerebral symptoms and died of metastatic choriocarcinoma. The lack of response in this patient, we felt, lay in the atypicality of the lesion. The folic acid antagonists have been administered to chorionic gonadotropin-producing tumors. While this last case is histologically a trophoblastic tumor, it was not a chorionic gonadotropin-producing tumor since repeated

serum and urine tests have always been negative. This one freakish characteristic of this particular tumor, we feel, may be the reason for the failure of amethopterin therapy.

Comment

The antifolic preparation, amethopterin, is the first drug that has shown beneficial effect on cases of choriocarcinoma. In the past, we tried many other modalities to no avail. While our cases have been recent and these patients have to be followed for a longer time, we feel that at last we may have an agent which, while not curing all cases, has cured a few and brought about arrest or partial cure in others. In some special cases and with close and adequate supervision, it is conceivable that it may do away with hysterectomy in those cases of chorioadenoma where the patient is young and childless. Certainly, the practice of performing a hysterectomy in the woman who continues to bleed even after repeated curettage and has a rising titer of chorionic gonadotropin hormone in the absence of lung or other obvious metastases may be done away with until after a fair therapeutic trial with amethopterin. We feel that in this respect amethopterin should bring about a modification in our time-honored treatment of hydatidiform mole and suspected choriocarcinomas. How really effective amethopterin will be in the treatment of choriocarcinoma only time will tell. So far it has helped in a few cases, but we feel the patients we have treated so far are too few to evaluate the drug properly. We would be remiss if we did not emphasize that the drug is toxic and should be used judiciously.

Summary

1. Three patients with histologically confirmed chorioadenoma destruens with extension and a patient with probable chorioadenoma were treated with amethopterin and all may be considered cured.
2. Twelve patients with histologically proved choriocarcinoma with metastases were treated with amethopterin. Five after

3 years are clinically normal. These represent a 41 per cent 3 year salvage. Four patients with choriocarcinoma with metastases, after repeated courses of amethopterin treatment, have shown considerable improvement but still show residual lesions during a follow-up of 1 to 2 years. Three patients died from

drug toxicity during the course of this 3 year study.

Acknowledgment is made to Zuellig and Company, Manila, and the Lederle Laboratories for the use of some of the amethopterin (Methotrexate) used in this study.

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Uterine choriocarcinoma treated with operation and amethopterin

Report of a case

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AMONG the malignant neoplasms arising from the female reproductive tract, choriocarcinoma is one of the most resistant to the usual methods of therapy. When extension of the tumor beyond the confines of the uterus is clinically detectable at any time, disappointing results have usually followed treatment with radical operation, ionizing radiation, steroid hormones, radiomimetic drugs, or any combination of these agents.

Possible dividends to be accrued from adjunctive chemotherapy have been highlighted by the investigations of Hertz and his colleagues^{3, 12} into the effect of anti-folic acid drug therapy upon far-advanced trophoblastic neoplasms. Impressed by the preliminary reports, we employed one such drug, amethopterin (4-amino-N-10-methyl-pteroyl-glutamic acid; Methotrexate), as therapy for an inoperable mass residual in the pelvis following a hysterectomy for uterine choriocarcinoma.

A 25-year-old Negro woman, gravida v, para v, was referred to University Hospital in February, 1959, with the following history: In August, 1957, she had been delivered of a normal term infant at another hospital. Several weeks after delivery, she began to have daily vaginal spotting and light bleeding. A curettage in February, 1958, obtained tissue which proved to be normal proliferative endometrium, but she continued to

bleed irregularly thereafter. Between April, 1958, and February, 1959, she was hospitalized on 5 separate occasions at which times curettage and whole blood replacement were thought necessary. From July, 1958, onward, the clinical picture at the time of each admission was characterized by significant temperature elevation, vaginal bleeding, evidence of marked acute and chronic blood loss, and progressive weight loss.

In view of the discovery of necrotic decidual and trophoblastic tissue in repeated endometrial curettings since July, 1958, as well as the failure to unearth evidence of systemic disease which could explain the clinical picture, a tentative diagnosis of repeated septic abortion was made by the attending physicians. In retrospect, it is probably significant that no chorionic villi have been demonstrated on subsequent review of the curettement sections.

On Jan. 18, 1959, the patient returned to the hospital with fever and vaginal bleeding. A mass in the upper vagina was noted and biopsied. Histologic examination revealed choriocarcinoma. Intravenous pyelography showed no abnormality of the urinary tract.

Six uterine curettements and 6,000 c.c. of whole blood replacement had been required from April, 1958, to February, 1959. A 40 pound weight loss had been a prominent feature of her illness.

On Feb. 4, 1959, the uterus was enlarged to the size of a 16 to 18 weeks' pregnancy. It was irregularly softened and displayed a marked irregularity of the left cornual surface. A vaginal mass, covered by intact epithelium, occupied the left lateral fornix and the paravaginal tissue adjacent to the upper three fourths of the left

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anterolateral vaginal wall. This ovoid mass was rubbery in consistency and nontender. It was palpable abdominally where its upper border could be outlined 1 cm. superior to the medial third of the left inguinal ligament.

A search by x-ray for metastases was negative. Urinalysis and blood studies revealed no significant abnormalities. The human chorionic gonadotropin titer was 60 I.U. per cubic centimeter of serum. On Feb. 5, 1959, an exploratory operation was performed on the abdomen. The abdominal cavity was entered through a low transverse incision and no evidence of pathologic conditions outside the pelvis was encountered. The uterus was enlarged and protruding from its surface were several masses of friable, dark red tissue to which the omentum was attached (Fig. 1). The mass replacing the left paravaginal tissue was easily palpable and lay immediately adjacent to the bladder. No other extrauterine tumor was noted. The metastatic mass was covered by the peritoneum of the pelvic floor.

A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The only difficulty encountered was bleeding from the posterior surface of the bladder. Blood replacement totaled 1,500 c.c. An adequate excision of the metastatic mass would have necessitated a total cystectomy and urinary diversion.

Following operation, daily serum human chorionic gonadotropin concentrations were obtained. The serum concentration decreased to a level of 30 I.U. per cubic centimeter of serum by February 9, and thereafter maintained itself at this level. No postoperative complications were encountered. On February 16, the human chorionic gonadotropin serum concentration and

the vaginal mass remained unchanged, and amethopterin administration was begun. For the first 2 days, 5 mg. was given twice a day intramuscularly. Thereafter, the same dosage was maintained orally without interruption.

The serum level decreased after the first day of amethopterin intake to negative on February 19. Thereafter, neither urinary nor serum chorionic gonadotropin could be demonstrated.

Amethopterin was administered until March 3, at which time it was discontinued because of the appearance of toxic signs and symptoms (stomatitis, nausea, and vomiting). During the 16 day period of drug intake the white blood count fell from 19,200 to 7,300, the platelet count from 1.8 million to 0.64 million, and the reticulocyte count from 5.4 to 1.6 per cent.

The patient was discharged on March 7, at which time no appreciable change in the size or consistency of the metastatic mass was detectable.

Microscopic findings.

Vaginal mass. Sections of the preoperative biopsy of the vaginal mass revealed widespread coagulation necrosis of smooth muscle; multiple areas of muscle and stroma were infiltrated by columns and masses of trophoblastic cells; syncytial and cytotrophoblastic elements were both present in approximately equal proportions; no chorionic villi were present in multiple sections made at various levels; a diffuse chronic inflammatory response was noted within and around the trophoblastic masses, and massive interstitial hemorrhage was seen at all levels (Fig. 2).

Surgical specimen. Blocks taken from the softened tumor masses protruding from the external surface of the uterus and from within its wall yielded a histologic picture indistinguishable from that seen in the vaginal biopsy sections; no chorionic villi were found in multiple sections of each block, and sections of tubes and ovaries were histologically normal (Fig. 3).

In the unanimous opinion of the pathology board, the criteria for an acceptable histologic diagnosis of choriocarcinoma had been met.¹

Follow-up. The patient was examined and had blood drawn for a frog test every 2 weeks for 2 months postoperatively and, thereafter, at intervals of no more than one month. On March 25, 1959, the vaginal mass was felt to be definitely softer and slightly smaller than noted at the time of hospital discharge. On April 22, the vaginal mass was no longer palpable and, since that time, repeated pelvic examinations have confirmed its absence.



Fig. 1. Intact surgical specimen demonstrating the expanded corpus and the tumor mass protruding from the fundus.

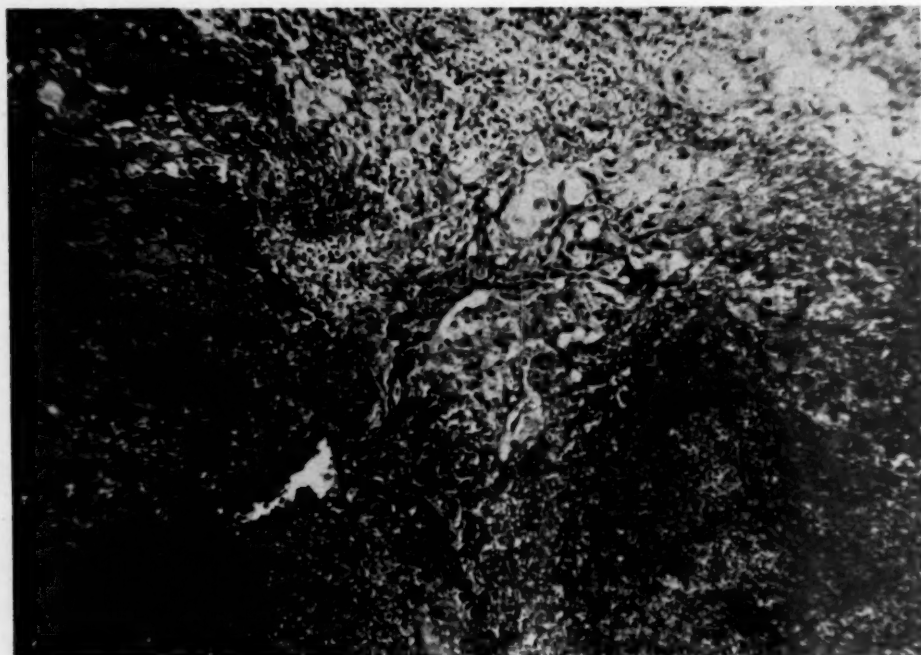


Fig. 2. Medium-power view of representative section made from vaginal wall biopsy. Large clump of trophoblastic cells at center is surrounded by necrotic muscle and fields of red blood cells.

At the time of this report, over one year after therapy, she has regained more than 25 pounds of the lost weight, feels entirely well, and presents no clinical or laboratory evidence of residual or recurrent neoplasm.

Comment

Our case is presented at this early date for the following reasons: First, with respect to choriocarcinoma, a one year survival without evidence of disease, perhaps even a 6 month survival, seems to have prognostic significance equal to that of a 5 year survival following treatment for many other malignant tumors.² Second, a modification of the generally recommended dosage schedule for amethopterin is outlined (Fig. 4).

Our decision to institute chemotherapy postoperatively was made when the human chorionic gonadotropin serum concentration leveled off at 30 I.U. per cubic centimeter and was maintained for one week. As indicated in Fig. 4, theoretical values for human chorionic gonadotropin clearance would lead one to expect a continued decline in concentration until, on or about the third or fourth postoperative day, values would be undetect-

able by our method. This assumption is valid if all functioning tumor is presumed to be removed by operation.⁵ The failure of human chorionic gonadotropin serum levels to follow this pattern confirmed our impression that the paravaginal tumor was viable. Moreover, the absence of palpable change in this mass and the maintenance of the serum hormone concentration for one week failed to suggest the early degenerative change in the metastasis which has been reported in some cases after surgical removal of a primary choriocarcinoma. A further period of observation was felt unjustified.

The major point of difference between the management of this case and those reported previously is to be found in the modified dosage regimen. The schedule developed by the group at the National Institutes of Health and adopted by other reporting parties calls for intensive, intermittent dosage.¹² This is initiated by the administration of amethopterin in a dosage of 1.0 to 4.5 mg. per kilogram of body weight as a single intravenous dose. Two weeks later, the drug is readministered over a 5 day period at a

level of 0.5 mg. per kilogram per day in divided oral or intramuscular doses. These 5 day courses are repeated at intervals of 2 weeks until there is a remission of disease, or drug toxicity dictates discontinuance. This intensive regimen interposed between periods of rest is predicated upon the expected reversibility of toxic effects in normal host tissue and the possible failure of such reversibility in tumor tissue after repeated courses.¹² The decision to employ much larger doses than those previously found so useful in certain leukemic states seems to have been prompted by a clinical study reported in 1951. This demonstrated the ineffectuality of protracted small-dose therapy in the treatment of many different malignant neoplasms, excepting only leukemia.⁶ Significantly, however, trophoblastic neoplasms were not studied in that report. There is ample evidence, both clinical and experimental, demonstrating the exquisite sensitivity of embryonic tissues to the destructive effect of anti-folic acid drug administration.^{7, 8} Furthermore, presently available clinical evidence indicates that destruction of tumor without concomitant destruction of vital normal host tissue is difficult to achieve when intensive dosage

regimens are utilized.³ There is tremendous individual variation with respect to normal tissue tolerance to this drug and this must be considered in light of the knowledge that peak toxic response to the intensive 5 day course of therapy is not manifested until 4 to 7 days after the drug has been discontinued.³ All investigators confess almost complete inability to prevent the drug's effect after absorption by the patient and, more significantly, equal inability to effectively reverse serious host toxicity when this is manifested. This seems to invite disaster in those individuals whose tissues are especially sensitive to the drug. That these are by no means uncommon is indicated by the reporting of one definite death caused by drug toxicity and 3 other cases in which the drug was believed to contribute significantly to death in one treated series.³ Similar untoward effects have apparently been encountered during other clinical trials of this drug.^{9, 10}

In view of these reports, we wished to minimize, if possible, the risk of inducing fatal drug toxicity. It was thought advisable to administer a considerably smaller daily dose than that recommended and to repeat this without interruption until either a clinical

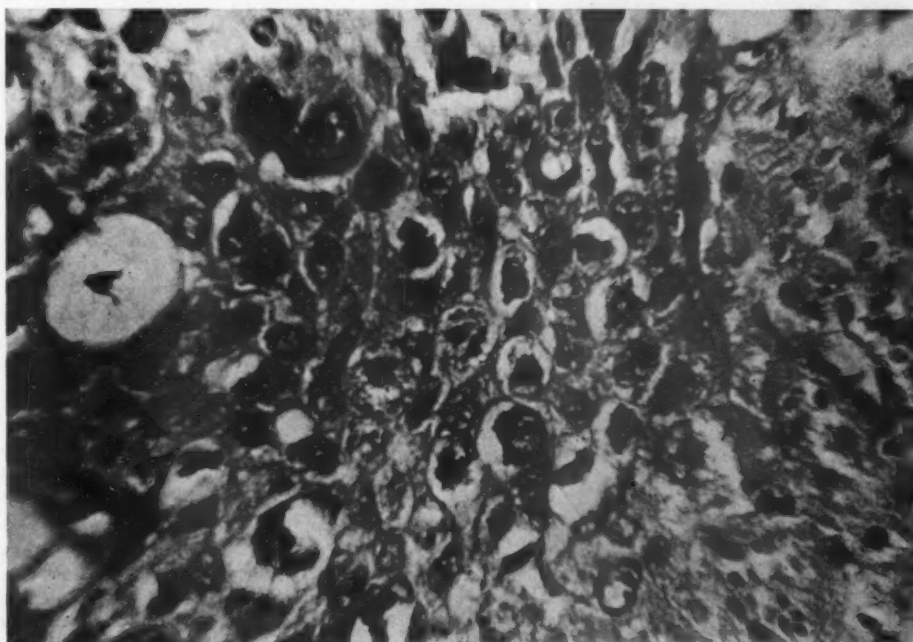


Fig. 3. High-power view of section from uterine wall showing a field of trophoblastic cells, mainly cytotrophoblast, in this particular area.

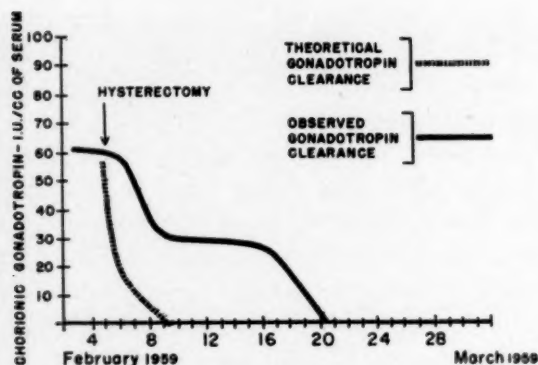


Fig. 4. Human chorionic gonadotropin blood levels throughout treatment with operation and amethopterin administration.

remission or early signs of drug toxicity were manifested. This regimen has been shown to be effective in the treatment of acute leukemias.⁶ The risk of developing tumor resistance to the drug during the protracted regimen was balanced, we believed, by protection afforded against massive, irreversible host tissue damage. The daily dose was accordingly adjusted and amounted to 10 mg. per day (0.16 mg. per kilogram of body weight).

The role played by amethopterin in effecting the good result is not clear at the present time. Spontaneous regression of metastatic choriocarcinoma has been reported after removal of the primary tumor in the past, perhaps more commonly than in the case of any other type of neoplasm.¹¹ Nevertheless, such happy occurrences are relatively uncommon; certainly not so common as to justify withholding supplementary treatment, if it is reasonably risk free in itself.

The number of complete remissions in Hertz's series is small, but impressive, when consideration is given to the generally poor condition of the patients. All of the patients were proved to have disseminated disease, most evidenced serious degrees of systemic deterioration, and a number of them were practically in a terminal condition when admitted to the study unit. It will be recalled that even those who eventually succumbed to the disease evidenced at least temporary dérangement of tumor metabolism as re-

flected by significantly lowered output of human chorionic gonadotropin.²

Accumulating evidence, therefore, justifies the statement that anti-folic acid drugs are able to inflict fatal damage to either normal or abnormal human trophoblastic tissue without necessarily causing irreversible destruction of normal host tissues. Whether or not a tumor can be damaged beyond its power to recover is unpredictable in an individual case and will depend not only upon the sensitivity of the tumor to the drug, but also upon such other factors as the quality of poorly understood natural host resistance mechanisms and the drug sensitivity displayed by normal host tissues.

Summary

A case of metastatic uterine choriocarcinoma, proved by tissue biopsy, has undergone complete remission for more than one year following surgical excision of the primary tumor supplemented by a single course of protracted amethopterin therapy.

The recommended amethopterin regimen was modified in this case for the reasons stated.

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Blood group factors in women with choriocarcinoma as compared with those of their husbands

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With the technical assistance of

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CHORIOCARCINOMA and related trophoblastic tumors are of fetal origin. The genetic composition of the cells of these tumors is thus derived from paternal as well as maternal sources and the wife is host to a tumor containing antigen derived from her husband. This study was undertaken to determine whether there was any immunologic response in the mother to these foreign antigens in a manner similar to the response to the exposure to Rh antigens which results in erythroblastosis fetalis. Such a response could be related not only to the etiology of the tumor state but also to the spontaneous regressions¹ which are noted in the natural history of this disease.

Accordingly, we have made a comparative study of the maternal and paternal blood factors in 28 cases of histologically proved choriocarcinoma or chorioadenoma destruens. These patients were admitted to the Clinical Center of the National Institutes of Health in connection with chemotherapeutic studies previously described.^{2, 3} They were, with few exceptions, in the advanced

stage of progressive, metastatic disease. Hence, it may be considered that the host exposure to the fetal tumor tissue would have been ample to permit active antigen exchange.

Experimental

Whenever possible, clotted blood samples were obtained from patients and their husbands at the same time so that the samples could be tested in parallel.

The tests included blood grouping by the method of choice for the reagent used, and a test of the maternal serum for antibodies to paternal red blood cells by the saline and antiglobulin (Coombs) technique.

Results

The results of testing all 28 of these patients and their husbands for the blood factors listed in Table I show no great differences from an expected distribution.⁴ The frequencies of gene combinations for Rh as compared with the expected distribution are given in Table II.

It is important in considering possible immunologic responses in the patients to know the extent of antigen disparity between the paired marriage partners. In Table III are listed, for each antigen, the number of cases in which the husband had

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Table I. Presence of blood group factors

	Blood group				M	N	U	P	rh' C	rh'' C ^w	Rh ₀ D	Rh ₀ D ^w	rh'' E	hr' c	hr'' e	K	k	Fy ^a
	A	B	O	AB														
Observed																		
Patients	13	1	13	1	23	26	28	21	20	0	25	0	13	23	28	5	28	23
Husbands	10	3	14	1	24	22	28	20	22	0	26	1	12	26	25	3	28	20
Expected	13	2	12	1	22	20	28	22	19	0	24	0	8	23	27	3	28	18

Table II. Probable Rh genotypes

	rr (cde/ cde)	R ₀ r (cDe/ cde)	R ₁ r (CDe/ cde)	R ₁ R ₁ (CDe/ CDe)	R ₂ r (cDE/ cde)	R ₂ R ₂ (cDE/ cDE)	R ₁ R ₂ (CDe/ cDE)	R ₁ r (CD ^w e/ cde)	R''r (cDE/ cde)
Observed									
Patients	2	1	7	5	4	0	8	0	1
Husbands	1	1	11	2	1	3	8	1	0
Expected	4	1	10	5	3	1	4	0	0

Table III. Extent of antigen disparity

	A	B	M	N	P	rh' C	Rh ₀ D	rh'' E	hr' c	hr'' e	K	Fy ^a	Total
Possible immunization													
Husband has antigen not present in patient	4	3	4	1	6	6	3	7	5	0	2	4	45
Control													
Patient has antigen not present in husband	7	1	3	5	7	4	1	8	2	3	4	7	52

an antigen not possessed by the wife. In such a situation the tumor host (wife) might also be host to erythrocyte antigens (from the husband). Also listed as a control are the number of times the wife had the antigen and the husband did not. Since these pairs are presumably somewhat racially matched, this latter serves as a parallel control in each case. The resultant figures for antigen disparity show no unexpected differences between the patients and their controls.

The sera of all patients were screened for antibodies to blood group factors which might have been stimulated by the implantation of fetal antigens derived from the husband. Only 1 of the 28 patients had irregular antibodies. This was anti-Kell which was found in a patient whose husband did not have the Kell factor. The

source of stimulus was, therefore, presumably one of her previous transfusions and unrelated to the disease proper.

In 2 cases it was possible to test the blood groups of children who were presumably the product of the pregnancy which went on to result in a choriocarcinoma. Neither child had antigens not already present in the mother, and the maternal sera contained no antibodies against the child's red blood cells.

Comment

The data presented should be considered with two recognized limitations. First, it was not always possible to test patient samples when they were free from transfused blood. Half of the patients had had more than one transfusion within the 3 months prior to testing. This might, of course, re-

sult in false-positive findings in all tests, but probably not for ABO groups and Rh₀ (D) types. The high values for the controls in Table III, i.e., antigens present in the patients but not present in their husbands, illustrate this point. Even in these patients, the data relating to lack of antibodies to the husbands' red cells remain significant. Second, the patients, because of the nature of the disease, were in some cases being treated with amethopterin. As a metabolic antagonist, this drug could depress antibody formation⁵ and lead to false-negative findings for irregular antibodies. There is no evidence that these limitations affected the generalizations made above, and these data, therefore, indicate a negative correlation between the blood factors of patients suffering from choriocarcinoma and those of their respective husbands.

Although the fetal trophoblast is a primitive and undifferentiated tissue, fetal red

blood cells have been demonstrated to possess the Rh factor at the age of 6 weeks.⁶ The data presented here relate to the red blood cell factors only, and the possibility that tissue antigens of tumor origin may effect the formation of antibodies other than those found capable of attaching to the red blood cells remains for further investigation.

Summary

Comparison of the blood group factors in 28 patients with choriocarcinoma or related trophoblastic tumors with those of their husbands revealed no evidence of maternal immunization by the fetal tumor tissue.

We acknowledge our gratitude to Dr. Philip Levine for his assistance in verifying many of the results through the technical help of Jane A. White of the Ortho Research Foundation.

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Choriocarcinoma

An unusual case recurring 9 years after subtotal hysterectomy and followed by spontaneous regression of pulmonary metastases

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THIS case illustrates two peculiar features of choriocarcinoma, which have long been considered controversial: (1) a long period of latency of trophoblastic cells and (2) spontaneous regression of extensive pulmonary metastases.

R. H., a 51-year-old housewife, gravida viii, para vi, was first seen in our clinic on Oct. 5, 1954, with the chief complaint of vaginal bleeding.

Menarche had occurred at the age of 15 years, and the menstrual periods had been regular and painless every 30 days until the age of 42 years, in 1945. She had had 6 normal deliveries between the years 1923 and 1936. The seventh pregnancy (in 1939) was artificially interrupted and the last one (in 1945) ended in a chorioadenoma destruens, which occurred 9 years prior to this admission to the hospital.

On April 2, 1945, after 5 weeks' amenorrhea, the patient noted persistent bleeding and consulted a gynecologist. After the diagnosis of incomplete abortion was made, a curettage was performed. The tissue removed was found to be a hydatidiform mole. The bleeding then recurred and 6 months later a supravaginal hysterectomy was carried out at another hospital for removal of a uterine tumor, which on microscopic examination was found to be chorioadenoma destruens. Thereafter amenorrhea followed and no abnormalities were detected.

On Oct. 3, 1954, she felt a sense of tension in the hypogastrium and on the morning of

October 5 vaginal bleeding began. She complained of nothing else. Examination on admission, October 12, revealed her to be slightly pale, but well nourished. Examination of the heart and lungs revealed nothing abnormal. The blood pressure was 130/60. The abdomen was slightly bloated, but no mass could be palpated.

Pelvic examination revealed normal external genitals. When a speculum was inserted into the vagina, blood-stained discharge was encountered. The portio appeared hypertrophic and a dirty ulcer was seen on the posterior cervical lip. Upon bimanual examination the corpus uteri was found to be absent, but on anal examination a firm mass 7 to 8 cm. in diameter was palpated which extended from the cervical stump and adhered to the anterior wall of the rectum. Otherwise, the pelvic organs appeared normal to palpation.

Laboratory data on admittance included red blood count 4 million; white blood count 7,800; hemoglobin level 95 per cent; urinalysis normal; erythrocyte sedimentation rate 13.

The preoperative diagnosis was malignant tumor of the cervical stump. On October 12 a laparotomy was performed under spinal anesthesia. The corpus uteri and both tubes and ovaries were absent. An elastic tumor, about 7 cm. in diameter, which seemed at first glance to be a hematoma, arose from the cervical stump. The surface of the mass was covered with peritoneum. The tumor was carefully separated from the bladder wall and a trachelectomy performed with little blood loss.

The tumor was roughly spherical in shape, elastic and soft on the whole, rather sharply defined by a thin membrane, 8 by 7 by 5.5 cm. in size, and weighing 185 grams. Sectioning

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the mass (Fig. 1) showed the growth projecting into the cervical canal, which was considerably elongated and rather thin. Dark red and white patches alternated, the red parts consisting largely of blood.

Microscopically (Fig. 2), a large central area was seen, composed of hemorrhage and necrosis in which remnants of trophoblastic nuclei were still recognizable. Next to this area there was a zone in which round and polyhedral cells (resembling Langhans cells) were arranged in large islands or bands bordered by a thin layer of multinucleated giant cells (resembling mostly syncytial cells). The surrounding muscle and connective tissue was invaded and conglomerations of embolic trophoblastic cells were found lying in the lumina of vessels in the vicinity of the tumor. The syncytial elements, for the greater part, were characterized by an even distribution of vacuoles, and the cells of Langhans showed marked evidence of anaplasia. In the muscle tissue which was adjacent to the tumor elements, no clear fibrinoid layer was to be found. There were interspersed a few leukocytes (mainly lymphocytes). A villous pattern was nowhere observed.

Postoperative course. A Friedman test, made the next day, contained 100 rat units of chorionic gonadotropin per liter. On chest x-ray examination nothing unusual was noted. Nine days post-operatively the Friedman test was unchanged, the erythrocyte sedimentation rate was 44. On the fifteenth day the Friedman test was negative at 100 Rb.U. The patient was eating well and feeling much stronger and was discharged on the twenty-third day after the operation (November 4).

The patient was seen for follow-up examinations on November 8, December 1, and January 17. She was found to be entirely asymptomatic. The Friedman tests were always negative at routine levels. On February 24 she complained of hemoptysis (5 to 6 times daily) and slight dyspnea when at work since mid-February. Investigation of the sputum revealed no tubercle bacilli. Chest x-ray examination on this visit revealed numerous snowball-like shadows in both lungs, which were interpreted as metastases from the choriocarcinoma (Fig. 3). Moreover, the Friedman test, became positive again, the titer being as high as 100 R.U.

She was readmitted to our clinic on March 5, 1955, complaining of blood-stained sputum. At that time she looked slightly pale but well



Fig. 1. Gross specimen showing a large choriocarcinoma, which was derived from a cervical stump. (Front view of tumor.)

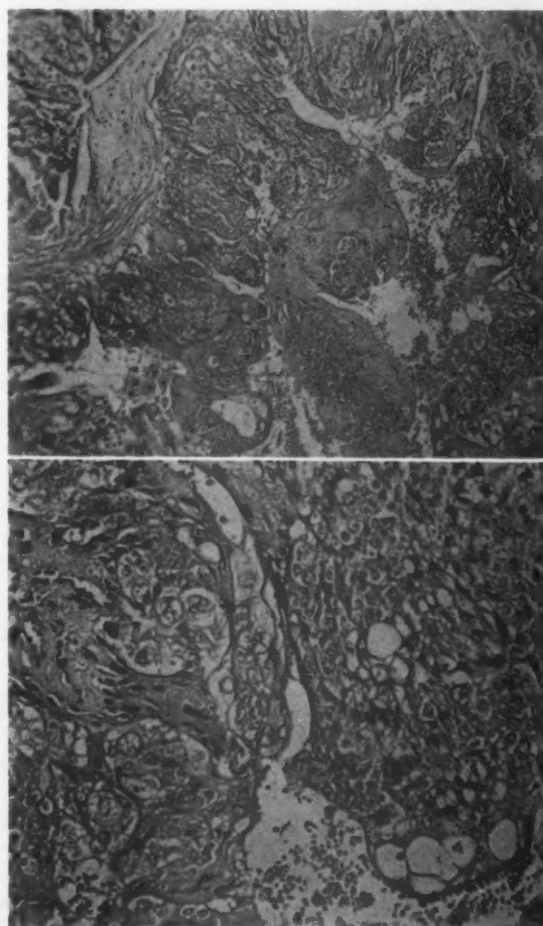


Fig. 2. Microscopic section of tumor at the periphery, showing great activity causing hemorrhages and necrosis. The pleomorphism of both kinds of trophoblast together with anaplasia and giant cells is obvious. (Hematoxylin and eosin. A, $\times 80$; B, $\times 200$; reduced $\frac{1}{4}$.)

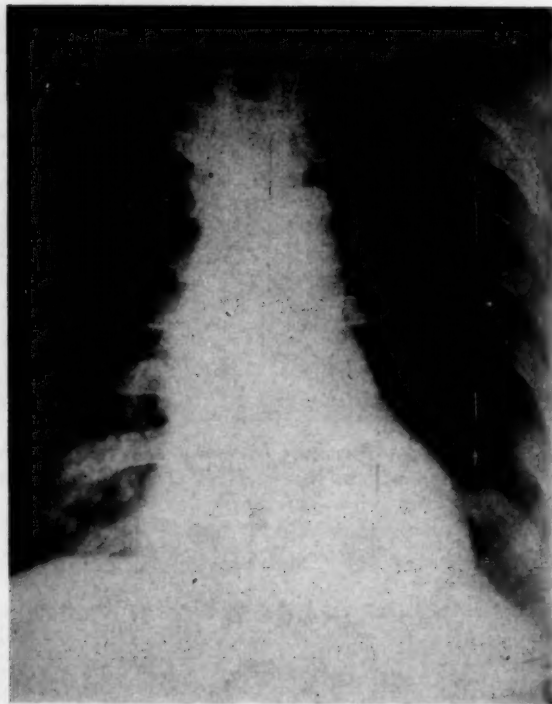


Fig. 3. Initial x-ray film of chest taken on Feb. 24, 1955, showing multiple metastases in both lungs.

nourished. Pelvic examination revealed no palpable pathologic condition.

Chlortetracycline was administered in view of the virus theory of the origin of the disease. Despite this treatment by March 9 the lesions spread considerably over both lungs (Fig. 4), and the chorionic gonadotropin titer of urine increased to 50,000 Rb.U. Though the x-rays and Friedman tests of March 23, April 6, April 20, and May 4 remained almost the same, her condition gradually deteriorated. The chlortetracycline was stopped on April 11, after she had received 47.5 Gm. As she wished to pass her last days at home, she was discharged.

On November 15 the shadows in both lungs showed remarkable increase (Fig. 5). Hemoptysis continued, attended by slight pains in the chest and in the lower part of the back.

On Jan. 2, 1956, she suddenly expectorated about 100 c.c. of blood but thereafter neither hemoptysis nor bloody sputum was seen.

By May 7, she was in a fairly good condition. She did not cough, though she had slight pains in the chest and waist, so we let her come to our clinic. Examination revealed no evidence of anemia. On percussion and auscultation both heart and lungs were revealed to be normal. The abdomen and the lower extremities were as

usual. Pelvic examination revealed no palpable disease. Complete blood count and erythrocyte sedimentation rate were normal. Chest x-ray examination showed complete disappearance of the shadows (Fig. 6), and the Friedman test was negative.

Follow-up examinations, x-rays, and Friedman tests between May 18, 1956, and Nov. 15, 1959 (3½ years after the disappearance of the shadows) revealed no abnormalities. She looked quite healthy and was able to do her work. She is considered completely cured.

Comment

1. **The long latent period.** It is not yet known how long trophoblastic cells in a maternal organism can live. Hitschmann² says that these cells cannot survive very long in the blood stream. The period of latency between the last delivery and the time when choriocarcinoma causes clinical symptoms is usually relatively short—in the majority of cases less than a year.

On the other hand, however, Ries¹¹ found placental villi in uterine vessels 18 years after the last delivery. Brown, Snodgrass, and Pratt¹ recorded a case of malignant chorion-

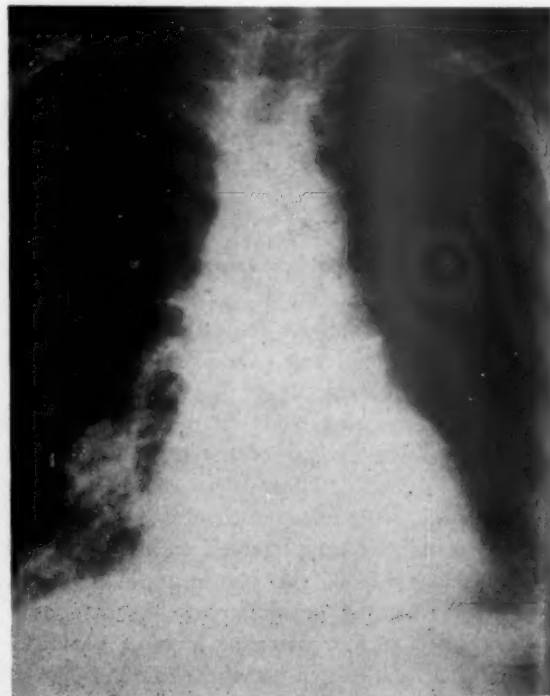


Fig. 4. X-ray film of chest taken on March 9, 1955, showing condition becoming worse.

epithelioma which stemmed from a mole which had been removed 8 years previously. Repeated curettage and panhysterectomy were performed 6 years prior to the first appearance of a pulmonary metastasis. Since the removed uterus in their case contained no chorionic tumor, they assumed that malignant chorionic elements must have been in a virtually dormant state in the lung during the entire period of latency.

Other cases with long latency have been recorded by Marchand¹⁵ (13 years), Lynch⁶ (31 years), White¹⁶ (19 years), Cristaller-Oppenheim¹⁵ (12 years), Suhonen¹⁵ (6 years), Mandelstamm¹⁵ (3 years), Feiner¹⁵ (2½ years), Salacz¹⁵ (3 years), Slavik¹⁵ (3½ years), and Maier⁷ (3 years).

Our patient was 51 years old. It is not rare for a woman in the menopausal age group to develop choriocarcinoma. Park and Lees⁵ reported a choriocarcinoma in a woman 55 years of age, 3 years after the menopause. White¹⁶ described a chorionepithelioma in the uterus of a woman aged 59 years, in whom artificial menopause had been induced by x-ray therapy 3 years and



Fig. 5. The shadows in both lungs showed a remarkable increase.

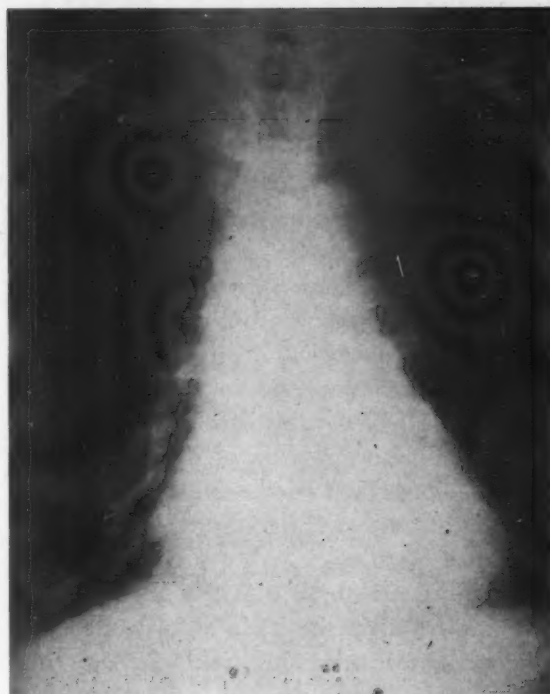


Fig. 6. X-ray film of chest taken on May 7, 1956, revealing complete disappearance of the previous pulmonary metastases seen in Figs. 3 to 5.

4 months previously. Ladreyt and Drugman⁵ observed one in a woman 63 years of age, whose last delivery was 19 years prior to the onset of the lesion. Schaamigs¹² saw one in a woman, aged 64 years, in whom menopause had occurred at the age of 42.

However, as women of advanced age are apt to deny their pregnancies, we cannot always give credit to the statement that the last delivery occurred in the remote past. According to Torggler¹⁷ women beyond the age of 50 become pregnant at the rate of 0.01 per cent. There has even been a case of pregnancy at the age of 63.¹⁸ Moreover, there remains the possibility in these cases that there may have been a more recent pregnancy which was unrecognized. And, too, we must always bear in mind the teratomatous chorionepithelioma which may occur even at puberty. Because of these complexities, Siegmund¹⁵ says that it is difficult to accept the possibility of long latency as being true. To the best of our knowledge, however, there is no evidence to disprove

the long latency in our case. Though a single case, it seems to exhibit this feature of the disease without any doubt, for these reasons:

1. A supravaginal hysterectomy with bilateral salpingo-oophorectomy had been performed 9 years previously. Therefore, an intercurrent pregnancy of any kind may surely be excluded.

2. The only other possibility would seem to be that of teratogenous origin, the choriocarcinoma having arisen in a teratoma of the uterus. However, this patient was gravida viii, para vi; no teratoma of the uterus had been previously recorded, and no histologic evidence to support the diagnosis of teratoma was found.

Therefore, we think that this lesion probably originated in the hydatidiform mole or in trophoblastic elements derived from the mole 9 years previously, and consequently a long latent period would seem to be established. Accordingly, the malignant chorionic elements must have remained quiescent in the cervix for 9 years, becoming activated later by some unknown stimulus.

2. Spontaneous resolution of the pulmonary metastases. In most cases, metastases appear a few weeks or, at most, a few months after the removal of the primary tumor. The pulmonary metastases in our case also arose 3 months after the operation. Besides, the common concept of the boundless malignancy of this lesion has been shaken since the complete resolution of a vaginal nodule brought about by simple enucleation has become known.¹⁹

Vaginal metastases are easily diagnosed, but dissemination elsewhere in the body, except for the lungs, is far more difficult to detect. This is because they are hardly determinable by means of x-ray examination. Regression of metastases in choriocarcinoma has been reported in 20 cases, and, of these, 12 were pulmonary in location. However, the majority of cases may actually represent either chorioadenoma or benign hydatidiform mole.¹³ Some of them are not acceptable because the evidence was based on the clinical symptoms alone, which could

have been due to pulmonary infarction or pneumonia.⁹

The only two examples with satisfactory evidence of spontaneous resolution are those of Lackner and Leventhal⁴ and Johnson,³ with a follow-up of 5 years and 15 months, respectively.⁹ We have had experience with spontaneous resolution of pulmonary metastases from chorioadenoma in 2 other cases.

The pulmonary metastasis appears clinically to simulate pulmonary infarction.² It is necessary, therefore, to determine whether proliferative elements are present in the embolus. The biologic urine test (gonadotropic titer) provides the only means of the differentiation.

In our case, the urine test became positive (100 Rb. U.) when the lung shadows were recognizable 4 months after the operation, resulting in a gradual increase of the titers with increase in the x-ray shadows. The test became negative again after resolution of shadows and remained so thereafter. On the other hand, the microscopic findings, above-mentioned, indicate decidedly that the primary lesion was a choriocarcinoma. Therefore, it is well substantiated that these lung shadows were not simple infarcts, but the metastases of choriocarcinoma.

Polano¹⁰ claimed that the prognosis in cases of long latency is entirely unfavorable and the mortality amounts to about 100 per cent. Schuster¹⁴ also says the latent period of chorionepithelioma following normal delivery is longest, that from abortion is next, and that from hydatidiform mole is shortest. He further says that the longer the latency the more unfavorable the prognosis. Our case, however, indicates the opposite to these views.

Do the long latency and spontaneous resolution in our case represent mere coincidence? Is there any correlation between them?

While it would be absurd to draw any conclusions from a single case, the sequence of events in this case might throw some light on the etiology of this most malignant tumor.

Summary

A case of choriocarcinoma with two unusual features is described: one is concerned with the 9 year dormancy of the tropho-

blastic elements, and the other with spontaneous regression of extensive pulmonary metastases originating from choriocarcinoma of the cervical stump.

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Hydatidiform mole with recurrent vaginal metastasis

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IN A study of trophoblastic lesions, it is important to recall that one of the normal functions of the trophoblasts is "invasion." The degree to which trophoblasts can invade the maternal tissue is determined by their proliferative and erosive capabilities to destroy the endometrium in which the fertilized ovum is embedded. Occasionally they invade the myometrium deeply, opening blood vessels and giving rise to physiologic metastases. These physiologic metastases occur more frequently in the lungs than in the vulva or the vaginal mucosa.

In this paper, we shall report a case of invasive mole with recurrent vaginal metastases in a young primigravida. The conventional management was not carried out, yet the patient survived and one year later gave birth to a normal infant.

Case report

The patient was a 22-year-old primigravida. Her family history was unremarkable and non-contributory. Past medical history was irrelevant except for the usual childhood diseases. (The patient had had no major infections or major operations.) The past obstetrical history was also unremarkable, with menarche having occurred at the age of 12, and menstrual periods every 28 to 30 days, lasting 3 to 4 days. She married at the age of 22 and became pregnant 3 months later. The patient had had regular menstrual periods up to 3 months before admission. The last menstrual period occurred in early June, 1956. She had not been feeling well since then

and the breasts had been sore. Two weeks after the last menstrual period, she experienced some slight vaginal bleeding followed by persistent nausea and vomiting which usually began in the earlier part of the day. Thereafter, she became markedly emaciated. The vaginal bleeding, which was at first slight in amount, became dark and sometimes brown and was made up of old blood.

The patient had been surprised by the excessive enlargement of the uterus. This disproportionately large size of the uterus for the stage of gestation, associated with the hyperemesis and the vaginal bleeding, led her family to suspect an "abnormal pregnancy."

Two months after the last menstrual period, and after one day of profuse vaginal bleeding, spontaneous expulsion of the mole occurred. Her family doctor admitted her to a private hospital for completion of the abortion by dilatation and curettage on Aug. 12, 1956.

Two weeks after this curettage, the profuse vaginal bleeding resumed and it was at this time that the patient came to see us.

On admission, she was markedly emaciated and anemic. The temperature was 100.2° F., the pulse was 110, the respirations were 22, and the blood pressure was 110/60. Physical examination revealed there were no abnormalities other than superficial 2 cm. vaginal nodule, elastic in consistency, bright red in color, and bleeding but not sensitive to motion, implanted on the posterior wall close to the perineum. The cervix was considerably softened and admitted a finger tip easily. The uterus was enlarged to the size of a 2 months' pregnancy, very soft and nonsensitive to motion.

Urinalysis, bleeding time, clotting time, and chest x-ray findings were normal. The red blood count was 2.33 million and the leukocytes 5,000.

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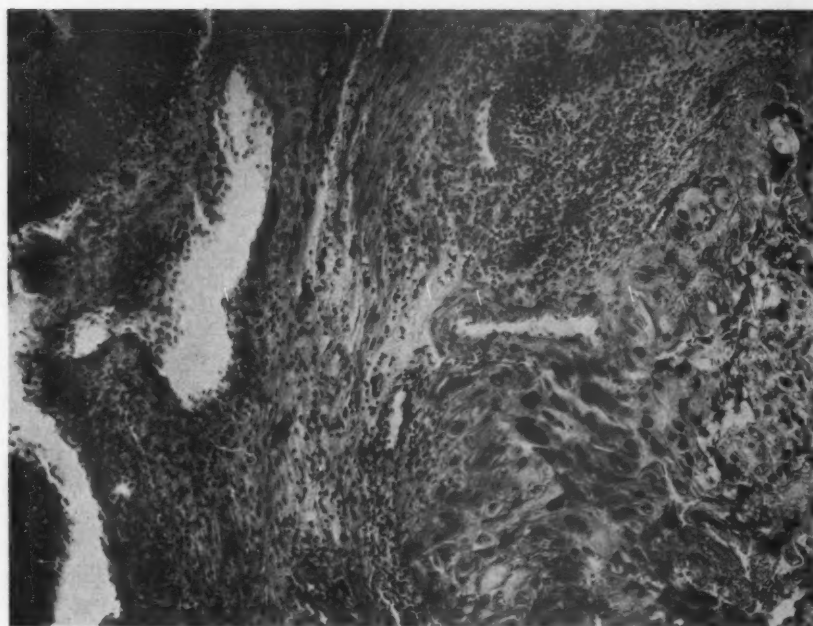


Fig. 1A. First vaginal metastasis. Islands of trophoblastic tissue, with cytotrophoblast and syncytium, under the normal vaginal epithelium.

The vaginal lesion was excised uneventfully and the patient was discharged on the twelfth postoperative day.

Microscopic section of the lesion showed trophoblastic tissue and well-preserved chorionic villi beneath normal vaginal epithelium (Fig. 1).

Postoperative bioassays for chorionic gonadotropin revealed the following values: September 9,700 U; October 1, 6,000 U; October 8, 15,000 U; October 10, 7,500 U; October 22, 7,500 U.

On Nov. 7, 1956, the patient was hospitalized for evaluation. The level of chorionic gonadotropin was unchanged, 7,500 UL. Examination at this time revealed, on the anterior wall of the vagina, a tumor of 2 cm. in diameter, elastic in consistency, bluish in color, and bleeding on motion. The tumor was excised the next day, and the operation was complicated by profuse bleeding. Microscopic sections showed proliferation of trophoblastic tissue which penetrated the musculature in places (Fig. 2). The diag-

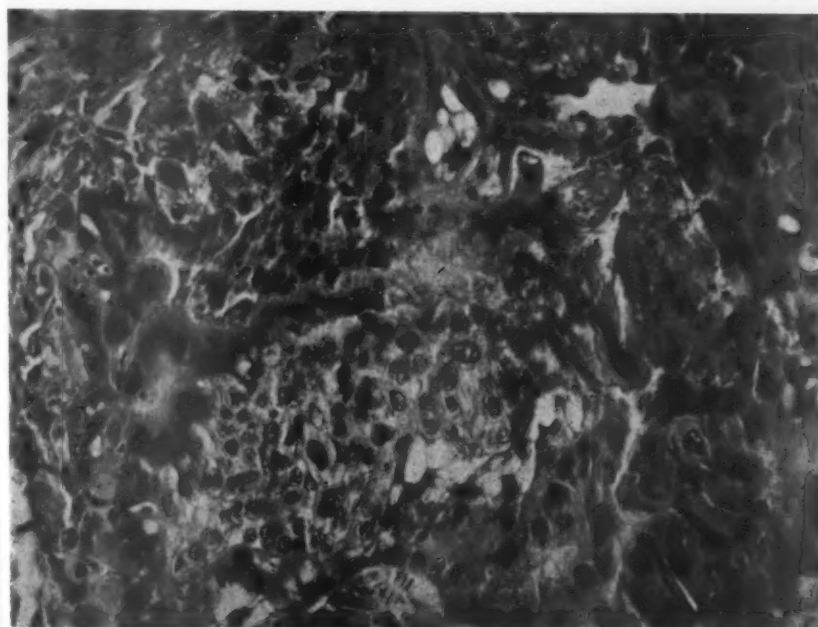


Fig. 1B. First vaginal metastasis. Higher magnification showing cellular detail.

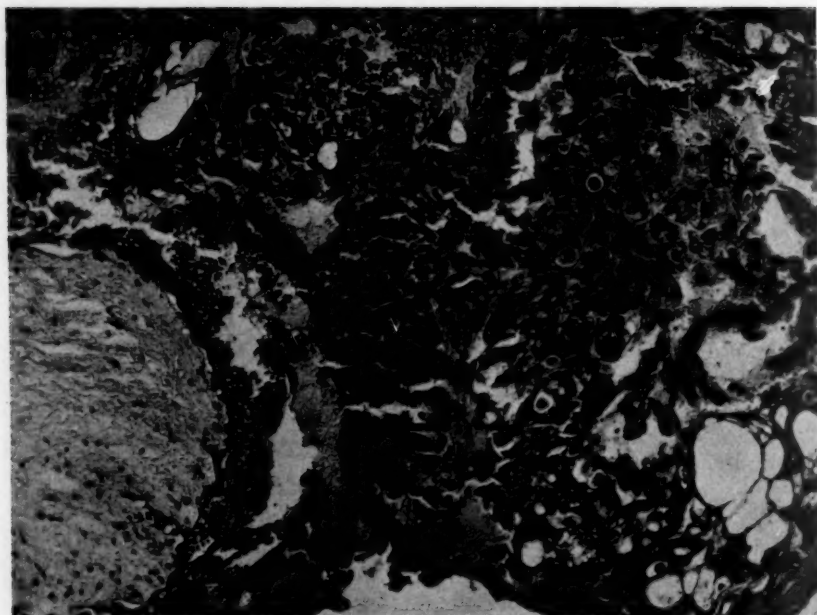


Fig. 2. Second vaginal metastasis. Proliferation of trophoblastic tissue resembling that of the first metastasis.

nosis of invasive mole was confirmed by Dr. Levaditi of the Institut Pasteur de Paris.

The chorionic gonadotropin titer, on Nov. 16, 1956, remained at the level of 1,000 U. Examination still revealed a uterus enlarged to the level of 2 fingerbreadths above the pubis.

A curettage was performed on Nov. 16, 1956. This showed syncytial endometritis with a few clumps of syncytium and some collections of cytotrophoblasts. Bioassays after this repeated curettage showed: December 10, 500 U; December 20, 500 U; January 1, 100 U.

On Jan. 1, 1957, pelvic examination revealed the uterus to be one and one-half times the normal size and elastic in consistency. No ovarian cysts were felt. Two pieces of tissue were removed from the site of the second vaginal metastasis. Microscopic examination of this showed no trophoblastic tissue.

During the next 6 months, the Friedman test was negative at monthly intervals. Eight months after the last negative Friedman test and examination, the patient returned (Feb. 24, 1958) because of amenorrhea of 2 months. The pregnancy test was positive and pelvic examination revealed a pregnant uterus of 2 months' size. The patient gave birth in September, 1958, to a normal infant weighing 2,600 grams.

Comment

We have reported a case of hydatidiform mole which invaded the blood vessels and

was transported to the vaginal wall twice. In spite of this repeat metastasis, we have discounted the malignant implication of this invasiveness. Indeed, invasion of blood vessels is a common property of moles. It gives rise to deportation and to dissemination. Schmorl¹ found placental cells in the pulmonary vascular bed of 80 per cent of 158 women who died during pregnancy from a variety of causes. Veit² and Poten³ also observed fragments of chorionic villi as well as isolated syncytial cells in the lungs.

With respect to vaginal invasion, it is generally accepted that the metastases of trophoblastic cells to the vaginal wall associated with mole, as in this case, usually represent retrograde venous embolization of trophoblast rather than autonomous secondary deposits. Ober⁴ feels that the so-called vaginal metastasis is not a sign of malignancy, but that, "This is largely a permeation of dependent venous channels by intravascular trophoblasts and that true infiltration of maternal tissue rarely occurs."

According to this opinion, our policy in the management of this mole with vaginal metastasis was to evacuate the mole vaginally, excise the vaginal metastasis, and follow the patient's condition by chorionic gonadotropin assay. The recurrence of vagi-

nal bleeding, the subinvolution of the uterus, and the persistently positive Friedman test were attributed to residual syncytial endometritis and trophoblastic tissue in the uterus. That the excision of the vaginal metastases and repeat curettage were followed by negative chorionic gonadotropin titers confirmed the impression of incomplete evacuation of trophoblastic tissue.

Novak and Seah⁵ concurred with our policy and thought that the conventional management with hysterectomy would not be justified unless the repeat curettage showed

a more highly suspicious malignant change, with broad fields of trophoblasts and no villi.

Summary

The case is reported of a young nullipara with invasive mole with two vaginal metastases. The therapy consisted of repeat curettage and excision of the metastases. The uterus was preserved and the patient survived to give birth 20 months later to a normal infant.

We are indebted to Dr. Eleanor Delfs for reviewing this paper for us.

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Cesarean section hysterectomy

A 10 year review

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CESAREAN hysterectomy performed in emergency situations is undisputed as a legitimate procedure. The controversy surrounding this operation in recent years seems to stem from two basic questions, namely, its safety in elective cases and its preferability to tubal ligation. The increasing number of reports on this subject indicates that more physicians are adopting cesarean hysterectomy when sterilization is indicated at the time of cesarean section. Conversion of this procedure from a strictly emergency basis seems to be correlated with the tremendous advance made in pre- and postoperative care and in anesthesia techniques.

Reports of large series are lacking in the literature, but the sum of smaller series is considerable. Our results in this series are in general agreement with those of other reports, and they indicate that cesarean hysterectomy is safer than heretofore assumed. It carries a morbidity and mortality rate not significantly higher than that for cesarean section with tubal ligation.^{3, 4, 9, 10, 11, 17, 18, 19, 21}

Much has been made of the fact that cesarean hysterectomy guarantees sterilization without the so-called "high" failure rate when tubal ligation is employed. Our feeling is that the difference in failure rate of

the procedures is not significant and therefore not worthy of consideration.

It has been pointed out that tubal ligation is much less effective at the time of cesarean section.^{1, 12, 13, 16} The reason for this is not known, but it is a flaw in the argument for the employment of this procedure at the time of cesarean section. We agree with the authors of the recent reports in favoring cesarean hysterectomy for elective sterilization; however, our main reasons are not quite the same and are not concerned with morbidity, mortality, or failure rates. Our chief reason for preferring this procedure seems to resolve from an affirmative answer to an almost philosophical question which we will discuss after presentation of our findings.

Materials and procedures

In the 10 year period beginning January, 1949, 272 cesarean hysterectomies were performed by the Independent Service at Charity Hospital of Louisiana at New Orleans. All were performed by residents of this service under staff supervision. Because teaching was involved during all operations no point was made of operating time. Among third year residents, however, familiarity with the procedure has reduced the average duration to between 1 and 1½ hours.

Of the 272 cases, 40 are subtotal hysterectomies. These were performed in the earlier years of the series, but since that

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time this method has been abandoned in favor of total abdominal hysterectomy. The remaining 232 cases were total hysterectomies, of which 65 were closed cuff and 167 open cuff procedures.

Since its introduction to this service in 1953 by Dr. Adolph Jacobs, the open cuff technique² has been the procedure of choice for all total abdominal hysterectomies. This technique calls for placing a continuous hemostatic suture around the cuff edge. The cuff is left open, and a "Y" drain is placed in the vagina with the short arms extending into the lateral subperitoneal areas. This allows any bleeding to present in the vagina and become immediately apparent to the operator.

The cases have been divided into indicated and elective groups following the classification devised by Sandberg.¹⁷ The elective group includes all cases in which hysterectomy, although considered indicated, was not necessary to save life. The elective cases include those performed for the deliberate sterilization of women who had had previous cesarean sections and those with benign lesions of the uterus. The indicated group includes cases in which the operation was necessary to save life and was performed regardless of the attitude of the physician or patient concerning cesarean hysterectomy. The indications for operation in this series are presented in Table I. All indicated cesarean hysterectomies were performed for uncontrolled bleeding. There were no patients in this series presenting carcinoma as an indication.

A revision of Sandberg's chart with more recent additions, including our own, is presented as Table II.

The average parity of patients in this series was 5. The average age of the patients was 30, but age was not considered an important factor if this procedure was deemed necessary.

Results

Maternal mortality. There was one maternal death, giving a percentage maternal mortality in this series of 0.37 per cent.

This patient died suddenly on the fifth postoperative day from a massive pulmonary embolus. This followed what was until that time a very benign postoperative course. The patient had had a previous cesarean section and was admitted with ruptured uterus, and so falls into the indicated category. We consider this complication to be incidental to the operation, as it is certainly not peculiar to this procedure.

Table I. Indications for hysterectomy

<i>I. Indicated</i>	
Couvellaire uterus (that did not contract)	17
Ruptured uterus (occult and obvious)	10
Extension of incision into uterine vessels	8
Uterine atony	4
Broad ligament hematoma	2
	41
<i>II. Elective</i>	
Previous cesarean section with grand multiparity	48
Previous cesarean section with leiomyomas	3
Two previous cesarean sections	85
Three previous cesarean sections	16
Four previous cesarean sections	2
Five previous cesarean sections	1
Grand multiparity	51
Miscellaneous benign lesions of uterus and cervix	24
Carcinoma of breast in grand multipara	1
	231

Table II. Modification of Sandberg's chart

<i>Author</i>	<i>Elective hysterectomies</i>	<i>Indicated hysterectomies</i>	<i>Mortality</i>
D'Esopo	45	9	
Mackenzie	35	6	
Cosgrove	24	31	2
Davis	128	12	
Dyer	138	52	2
Dodek	35	11	1
Siegel	12	2	
Weigle	24	2	
Bradbury	73	11	
Sandberg	90	7	
Hallatt	65		
Montague	76	27	2
Meyer and Countiss	86	15	
Alford, Miller, and Simpson	231	41	1
Total	1062	226	8

Operative complications. Two operative complications occurred which deserve special discussion. The first, uncontrolled bleeding, was successfully combated by unilateral or bilateral hypogastric artery ligation as indicated. There were 3 such cases. The second complication, inadvertent bladder penetration, occurred in 7 patients who had had low transverse cervical cesarean sections previously and who had dense adhesions which complicated the reflection of the bladder flap. All were successfully repaired by closure in layers and installation of an indwelling catheter for 10 days. The most important point concerning this complication is that it should be recognized at the time of operation.

The average amount of blood replaced per patient in the elective group was 700 c.c., and in the indicated group was 865 c.c.

Postoperative complications and convalescence

Postoperative complications. Postoperative complications and their incidence in this series are listed in Table III. A few deserve special mention.

Cuff hematomas occurred in 5 patients, or 1.85 per cent. Two patients (0.74 per cent) developed cuff abscesses. We attribute these comparatively low figures to the use of the open cuff technique with a vaginal drain.

Vesicovaginal fistula complicated 3 cases, or 1.1 per cent. Two were successfully treated surgically and the other healed spontaneously with conservative treatment.

One of the 2 patients sustaining pulmonary emboli died. The other recovered after a prolonged hospital stay.

Three patients were reoperated upon—2 for the control of intrapelvic bleeding and one for ligation of the vena cava for pelvic thrombophlebitis associated with embolic phenomena.

Convalescence. As to duration of hospitalization, there was a difference of only one day between the indicated and the elective groups. Mean hospital stay in days in the indicated group was 8.5; for the

Table III. Postoperative complications

Secondary closures	10
Pyelonephritis	8
Cuff hematoma	5
Vesicovaginal fistula	3
Cuff abscess	2
Stitch abscess	2
Pneumonitis	2
Pulmonary embolus	2
Drug fever	2
Wound separation	1
Retroperitoneal hematoma	1
Transfusion reaction	1
Superficial thrombophlebitis	1
Adynamic ileus	1
Wall abscess	1
Cystitis	1
Pancreatitis	1
Acute renal tubular necrosis	1
Levophed slough	1
Mastitis	1

elective group it was 7.6. This compares favorably with the average duration of hospitalization for laparotomy on our gynecology service.

Morbidity. Morbidity in this series has been classified arbitrarily as mild, moderate, or severe on the following basis: mild—temperature 100° F. or less; moderate—temperature over 100° F. but not over 101° F.; severe—temperature over 101° F.⁸ These elevations may occur on any postoperative day, including the day of operation. There were 89 mild, 105 moderate, and 78 severe cases of postoperative morbidity.

Table IV lists all diseases present at the time of operation. None was found to be a contraindication to the procedure.

Comment

Excessive blood loss is a frequently mentioned objection to cesarean hysterectomy. Blood is lost from two major sources during this procedure, the uterine incision and the undersurface of the bladder flap. The first is unavoidable, being a consequence of cesarean section. However, this may be easily controlled before hysterectomy by immediate closure of the uterine incision with a continuous through-and-through suture. The second source is more annoying. We have found that some operators have a

tendency to develop an unnecessarily large bladder flap with consequently greater bleeding. With experience, this problem lessens as the bladder flap is reflected only sufficiently to allow total hysterectomy. Also, hemostasis may be achieved, if necessary, in the routine manner by clamping and tying. It may be pointed out that a bladder flap is created for section and the decision to perform a hysterectomy does not appreciably increase bleeding in this area.

It has also been stated that the large size of the uterus has been a handicap. This, in our experience, has not proved to be the case. However, defundation following ligation of the uterine vessels may be rapidly and easily carried out.

A further objection to cesarean hysterectomy by some operators has been the increased vascularity of the tissues. In their opinion this makes the operation more dangerous. We have found the tissue planes easier to identify and dissection to be less difficult. Because of the vascularity, all pedicles are carefully inspected to assure complete hemostasis prior to reperitonization. Our staff feels that cesarean hysterectomy is technically far less complicated than the average laparotomy performed on our gynecology service. This is understandable in view of the large number of laparotomies performed for tuboovarian abscesses, large fibroids, and chronic pelvic inflammatory diseases.

In our experience the termination of menstruation has not been a problem to the patient. All patients have accepted the operation once the purposes and consequences are explained to them. We certainly agree, however, with those who feel

that the patient's attitude toward menstruation should be a primary consideration when she is a candidate for cesarean hysterectomy.^{3, 6, 14, 17}

Dyspareunia has not occurred in patients in this series. Vaginal length has been easy to preserve, and postoperative pelvic support has been adequate. Libido in many cases had been increased, probably because of the removal of the fear of pregnancy.

No effects on hormonal function resulting from hysterectomy have yet been definitely proved.^{5, 15, 17} Any that may be involved certainly must be on a long-term basis and cannot at this time be considered a contraindication to hysterectomy.

Gynecologic procedures for pelvic complaints developing subsequent to cesarean section with tubal ligation are common ranging from 6.8 to 24 per cent.^{15, 16, 20} This easily lends itself to charges of piecemeal surgery.

Finally, the removal of the uterus at this time, when it is no longer to be used for its primary purpose, reproduction, removes a potential site of future disease.^{7, 14, 17} This is especially important at this institution, where the patients are in a low economic bracket and have educational attainments of a similar level. For this reason it is difficult and many times impossible to impress upon these patients the importance of frequent examinations after sterilization.

Our feeling, then, is that there is insignificant difference between cesarean hysterectomy and cesarean section with tubal ligation from a standpoint of safety or effective sterilization. Knowing its relative safety we have chosen cesarean hysterectomy over the other methods of sterilization at the time of cesarean section because we have given an affirmative answer to the following question: Should a uterus deemed so diseased as to make further pregnancies unsafe be removed to protect the patient from future danger due to its presence? Each operator must, in view of all information at hand, answer this for himself.

Table IV. Concurrent diseases

Severe pre-eclampsia	47
Mild pre-eclampsia	27
Diabetes mellitus	9
Eclampsia	2
Cancer of the breast	
(with possible lung metastases)	1
Schizophrenia	1

Summary and conclusions

1. Two hundred seventy-two cases of cesarean hysterectomy at Charity Hospital of Louisiana at New Orleans have been presented. Forty were "indicated" and 232 were "elective."

2. Mortality in this series was 0.37 per cent. Morbidity is classified on an arbitrary basis. Complications of the procedure are discussed.

3. Solutions for the problems presented by this procedure are discussed.

4. Total hysterectomy at the time of cesarean section is a safer procedure than heretofore assumed and is the procedure of choice when sterilization is indicated at the time of cesarean section.

We wish to express our appreciation to Dr. Adolph Jacobs and Dr. Thomas Kramer for their generous assistance in the preparation of this paper.

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Cesarean section in a general community hospital

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PERIODIC analyses of cesarean section in various institutions are always timely and useful. However, when these are conducted in a general community hospital rather than in a highly organized clinic or medical center, the outcome may be more indicative of a general trend in obstetrical practice. While operators in the latter situation represent an acknowledged degree of experience, skill, and discretion, these elements vary to a greater extent with each specialist in private institutions. Any such investigation affords an opportunity to evaluate maternal and/or fetal risk.

Material

During the period between April 1, 1954, and April 1, 1959, 472 cesarean sections were performed at St. Elizabeth Hospital. The rate for the period under study was 3.43 per cent, with no evidence of the usual increment evidenced in general hospitals as reported by several authors.^{8, 17} Hall and associates,⁵ in reviewing cesarean sections in 10 hospitals associated with medical schools, found an incidence of 4.46 per cent (Table I).

Indications

The indications for cesarean section are listed in order of frequency in Table II. The rate according to indication in this study as compared to that in other investigations is shown in Table III.

Repeat cesarean section. Previous cesarean section was the indication for operation in

50.42 per cent of all cases during the 5 year period. Twenty-nine (6.14 per cent) of the women had had more than 3 previous cesarean sections. A cesarean section rate of 1.3 per cent at Duke University Hospital was reported by Ingram and associates.⁹ In their study, 33 per cent of the patients with post-cesarean uteri were delivered vaginally under close supervision with no instance of rupture. In 16,654 deliveries uterine rupture occurred in 13 patients, resulting in 5 maternal and 13 fetal deaths. The incidence of uterine rupture was 1 in 1,281 deliveries. The dictum "once a section always a section" was followed in most cases in the present analysis, as it is impossible to predict the ability of a uterine scar to withstand hours of active labor.

Primary cesarean section. The leading indication for initial cesarean section was cephalopelvic disproportion, existing in 105 (22.2 per cent) patients in this series. The majority were given satisfactory trials of labor. Seven patients had diagnoses of bony pelvic and/or spinal pathologic findings (Table IV). Two cases were placed in this category because of clinical impressions of ill-defined dystocia-dystrophy syndrome.

The second leading reason for abdominal delivery was primigravidity in the elderly patient. Twenty-four women were over 35 years of age (Table V). Thirteen were given trial labors, while definite evidence of cephalopelvic disproportion was found in 6 women. Three gave histories of previous pelvic operations. Cesarean section was performed on the remaining 2, ages 43 and 45, on the basis of age alone.

The next most frequent indications, with

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22 patients in each category and a 4.8 per cent frequency, were placenta previa and abruptio placentae. In the group with placenta previa the fetal mortality rate was 13.81 per cent; the rate in abruptio placentae was 45.45 per cent.

Abnormal presentation was the indication for cesarean section in 15 cases (3.2 per cent)

Table I. Cesarean section rate

	Hall and associates		Present study	
	No.	%	No.	%
Total deliveries	85,556		13,776	
Primary cesarean sections	2,219	2.59	226	1.68
Repeat cesarean sections	1,597	1.86	246	1.75
Total cesarean sections	3,816	4.46	472	3.43

Table II. Indications for cesarean section

Indications	No. of cases	Percentage
<i>Primary cesarean section</i>		
Cephalopelvic disproportion	105	22.2
Placenta previa	22	4.8
Abruptio placenta	22	4.8
Elderly primigravida	24	5.0
Abnormal presentations	15	3.2
Previous pelvic operations	8	1.6
Cervical dystocia	8	1.6
Prolapse of cord	7	1.4
Toxemia	5	1.1
Miscellaneous	18	3.7
Total	234	49.57
<i>Repeat cesarean section</i>	238	50.42
Total	472	100.00

Table III. Indications for cesarean sections in percentage, based on available reports since 1949

Authors	Repeat	Cephalopelvic disproportion	Placenta previa	Abruptio placentae	Toxemia
D'Esopo ¹	12.1	53.9	7.6	1.8	4.1
Kistner ¹⁰	22.71	51.0	6.77	5.58	3.19
Rubin et al. ¹⁶	46.1	15.5	5.7	6.8	—
Posner et al. ¹⁴	27.3	22.3	8.45	6.46	4.23
Gordon ³	35	34.7	11.1	4.8	4.3
Powell et al. ¹⁵	43.6	13.8	11.3	11.5	3.8
Hall et al. ⁵	41.9	21.5	7.4	7.2	10.2
Mean average	32.67	30.38	8.22	6.30	4.97
Present study	50.42	22.20	4.87	4.87	1.10

of all sections. Attempted conversions performed on most of these women were unsuccessful. Previous vaginal operations and myomectomy for infertility accounted for the procedure in 8 (1.6 per cent) patients. Cervical dystocia after 24 to 48 hours of labor was responsible for cesarean sections in an equal number of patients.

Primary cesarean section because of toxemia was performed on 1.1 per cent of the group. Despite therapy, symptoms in these 5 patients progressed and response to induction was poor. Miscellaneous conditions constituting an indication for operation are shown in Table VI.

Types of cesarean section. Various types of cesarean section were performed. Because of the high incidence (2 to 4 per cent) of uterine rupture in subsequent pregnancies following the classical procedure, this was used only 15 (3.18 per cent) times. Conversely, the rate of later rupture following the lower segment operation is only 0.25 per cent. This technique was used 426 (90.25 per cent) times. The low vertical method was used 31 (6.57 per cent) times.

Additional operations. In order of frequency the additional operations performed are listed in Table VII. While there is no unanimous opinion as to the removal of the appendix at the time of cesarean section, 156 appendectomies, with no resultant morbidity, were performed. Eight myomectomies and 6 incisional herniorrhaphies were performed. Hysterectomy was indicated in 5 patients because of Couvelaire uterus (1), placenta accreta (1), and ruptured uterine

scars (3). Pedowitz and Schwartz¹³ emphasized that disruption of the uterus occurs more frequently in the presence of more than one type of scar (transverse and vertical) in the uterus. Three silent uterine ruptures were successfully repaired. Multiparity was not an indication for hysterectomy. Three ovarian cysts, responsible for dystocia, were excised.

Anesthesia. Three hundred and sixty-one (76.45 per cent) patients were given general anesthesia, 347 receiving cyclopropane and 14 gas, nitrous oxide, and ether. Spinal anesthesia was employed in 108 cases (22.22 per cent). Two cesarean sections were performed under local anesthesia and one under hypnosis. There were no deaths or significant complications due to anesthesia.

Maternal morbidity and mortality. Morbidity was determined according to the international standard—temperature elevation to 38° C. (100.4° F.) on any 2 successive days after the first postoperative day. Forty-six (9.74 per cent) patients fell into such a category. Four women developed paralytic ileus; 5 were subjected to secondary incisional closure because of wound dehiscence.

During the 5 year period vaginal delivery accounted for an 0.027 per cent maternal mortality rate. Abdominal delivery during the period resulted in 2 deaths, a rate of 0.42 per cent. One patient died on the third postoperative day, following bronchopneumonia with right hydrothorax. The second woman was admitted during the seventh gestational month with a diagnosis of severe toxemia with nephritis and possible cardiovascular accident. Cesarean section was performed because of deterioration of her condition. She died in the recovery room.

Fetal outcome. Knowledge of the fate of infants delivered abdominally is always a point of clinical and academic importance. In the presence of an urgent maternal and/or fetal indication, the uncertainty of prematurity must be accepted. During the period under study 49 infants weighing less than 2,500 grams were delivered by cesarean section. Reasons for the operations in order of frequency are shown in Table VIII. Fetal

Table IV. Bony pelvic and spinal pathology

Fracture of the pelvic bones	2
Osteomyelitis of pelvis and spine	1
Tuberculosis of hip and spine	1
Poliomyelitis with spinal fusion	1
Pelvic rickets	1
Kyphoscoliosis	1
Total	7

Table V. Age and number of elderly primigravidas

Age of patients	36	37	38	39	40	41	42	43	44	45
No. of patients	3	5	5	1	3	4	1	1	—	1

Table VI. Miscellaneous indications

Rh isoimmunization	3
Dystocia due to pelvic tumor	3
Fetal distress	2
Vasa previa	1
Cervical malignancy	1
Diabetes	1
Poor obstetrical history	7
Total	18

Table VII. Additional operations

Operation	No.
Appendectomy	56
Myomectomy	8
Herniorrhaphy	6
Hysterectomy	5
For ruptured uterus	3
For Couvelaire uterus	1
For placenta accreta	1
Ovarian cyst	3
Repair of silent rupture	3
Removal of bicornuate horn	1

Table VIII. Cesarean section on infants weighing less than 2,500 grams

Placenta previa	14
Elective repeat section	12
Abruptio placentae	12
Fetal distress	4
Toxemia	2
Cephalopelvic disproportion	2
Ruptured uterus	1
Prolapse of cord	1
Diabetes	1
Total	49

Table IX. Uncorrected perinatal mortality in cesarean section

<i>Authors</i>	<i>Years</i>	<i>No. of sections</i>	<i>Per cent</i>
Hall et al. ⁵	1950-1955	3,816	11.9
Hess ⁷	1953-1955	571	5.6
Erhardt and Gold ²	1954-1955	16,949	5.2
Pedowitz and Schwartz ^{12, 18}	1953-1957	1,433	7.8
Grossman and Benson ⁴	1940-1955	569	8.2
Harris and Nessim ⁶	1952-1955	1,153	3.29
Present study	1954-1959	472	4.88

loss totaled 23 infants. For purposes of review and comparison, the uncorrected fetal mortality in a number of published series is summarized in Table IX.

Comment

While great variations in the rate of cesarean section exist and the operation has grown increasingly safe for both mother and child, maternal and infant mortality rates continue to be higher for abdominal than for vaginal delivery. This may, however, be partially accounted for by the jeopardizing conditions necessitating abdominal delivery.

In the present analysis most primary cesarean sections were performed upon the correlation of x-ray pelvimetry and clinical judgment. In repeat cesarean sections consideration of the consequence of ruptured uterus influenced most operators in application of the dictum "once a cesarean section, always a cesarean section." In any situation, estimated date of confinement, size of the infant, and status of the cervix are evaluated before the type of delivery is selected.

Differences in perimortality rates are noted in Table IX. Landau and associates¹¹ attribute some infant loss in cesarean section to lack of respiratory conditioning, which the fetus naturally receives during normal labor and delivery. They found that, of all obstetrical complications resulting in cesarean sections and premature infants, only the infants in the diabetes and placenta previa groups showed an improvement over those delivered vaginally.

While broad principles based upon knowledge and experience can be applied to most situations, the minutiae surrounding each case will very frequently determine whether or not a cesarean section will be performed.

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Hemodynamic effects of cesarean section

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PRIOR to the past decade, cardiac disease was considered by many to be an indication for cesarean section in order to avoid the stress and strain on the cardiovascular system during labor. Serious doubts as to the validity of this idea began to appear in the early 1940's. In 1941, for example, Gorenberg and McGleary¹ pointed out that the mortality rate in patients with heart disease was significantly higher following section than following vaginal delivery. They also observed that cardiac decompensation rarely occurred during labor. This was one of the first reports advocating vaginal delivery as preferable for the pregnant patient with heart disease. As late as 1945, however, Sampson, Rose, and Quinn² advocated cesarean section as a means of avoiding the "physical work load" of labor. In recent years, largely through clinical experience, most authors have concluded that heart disease is not an indication for cesarean section and that it should be reserved for obstetric indications.

Data reported recently from our laboratories indicate that even though each individual uterine contraction produces an increase in cardiac output, there is no sustained increase following a normal first stage labor. Vaginal delivery, on the other hand, is accompanied by an increase in cardiac output of approximately 18 per cent.³ This is in contrast to the findings of Hendricks and Quilligan⁴ who reported an accumulative increase

in cardiac output of 35 per cent in late labor over that in early labor.

The dictum that cardiac disease per se is not a valid indication for elective cesarean section is now generally accepted on a clinical basis. There remains, perhaps, some confusion as to the relative effects of labor, vaginal delivery, and cesarean section on cardiovascular physiology. Before one can conclude that elective cesarean section or vaginal delivery is best suited for the patient with heart disease, a thorough knowledge of the effects of these various stresses on cardiovascular physiology must be obtained. In an effort to clarify further these hemodynamic alterations, we have studied the effects of elective cesarean section on the cardiovascular physiology using the dye dilution technique. This report presents the results of these studies.

Methods

In this study, as in the past, we have used the dye dilution principle as a means of measuring and calculating hemodynamic function. Our technique utilizing these principles has been presented in detail and anyone interested is referred to these previous publications.^{3, 5} We believe that the dye dilution technique of measuring cardiac output using Evans blue dye* is the most accurate method available at present.

Material

Normal obstetric patients of the Maternity Division of the City of Memphis Hospitals

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Presented in part at a meeting of the Society for Gynecologic Investigation in Cincinnati, Ohio, April 3, 1960.

*Evans blue dye (4 per cent) used in this study was furnished by the Warner-Chilcott Laboratories, Morris Plains, New Jersey.

were used in this study. They were near term with a history of having had one or more previous sections and were to be operated upon with this as the only indication. There had been no history, symptoms, or physical findings of cardiovascular disorders. The hematocrit was greater than 30 per cent and the blood pressure was normal in each instance. The first determination was done with the patient at basal conditions approximately 4 hours prior to the operation. The next determination was done immediately after completion of the section. This usually was within 1 hour of the actual delivery of the infant. A third determination was done on the seventh postoperative day. Patients having detectable contractions were excluded from the study for fear of introducing extraneous factors that could possibly affect the cardiac output.

Thirty patients who had low cervical sections and 2 patients who had cesarean hysterectomies were studied. Every effort was made for this series to be comparable with the previous series of patients studied for the effects of labor and vaginal delivery.³

Results

The individual cardiac output values for 30 patients who had low cervical cesarean sections and 2 patients who had cesarean hysterectomies are listed in Table I. These are expressed both as liters per minute and as milliliters per minute per kilogram of body weight. It is misleading to express hemodynamic data from pregnant patients in terms of body weight.⁵ The Evans blue dye does not circulate through the fetus, cord, or amniotic fluid. Therefore, the weight of this tissue is not taken into consideration when hemodynamic functions are calculated and if these functions are expressed in terms of body weight discrepancies are introduced. For this reason, a comparison of hemodynamic data should be made in terms of total volume changes. The percentage change (Table I) has been calculated on the output expressed as liters per minute. The cardiac output in the low cervical series increased on the average from 6.4 L. per min-

ute before operation to 9.1 L. per minute upon completion of the operation. This increase amounts to 45 per cent. By the seventh postoperative day, the output has decreased to 7.4 L. per minute. This lacks 1.0 L. per minute of being equal to average nonpregnancy levels which are probably reached around the end of the second postoperative week. By way of comparison, it is significant to note that the average increase in output seen in the 2 patients who had cesarean hysterectomies was 36 per cent or approxi-

Table I. Individual cardiac output values and percentage change

	Before cesarean section		After cesarean section		Increase (%)
		ml./ min./ Kg.		ml./ min./ Kg.	
	L./min.		L./min.		
Low cervical section					
1	4.4	71	5.6	98	27
2	7.1	94	11.2	160	58
3	7.4	115	8.0	137	8
4	4.7	77	7.4	132	57
5	4.7	60	10.3	138	109
6	5.7	103	9.2	187	61
7	4.0	81	7.3	159	82
8	6.4	101	10.4	180	62
9	4.9	91	8.7	176	77
10	6.9	126	7.1	136	3
11	7.6	164	8.0	180	5
12	10.1	179	10.6	198	5
13	9.5	150	7.7	123	-19
14	5.6	90	7.1	119	27
15	8.5	117	8.4	120	-2
16	4.3	69	5.7	102	33
17	10.0	183	9.3	187	-7
18	8.6	114	11.0	156	28
19	8.1	108	7.6	108	-6
20	5.9	116	6.8	147	15
21	8.8	126	8.5	133	-3
22	5.4	79	12.0	275	121
23	9.9	139	8.6	129	-13
24	6.5	112	10.1	192	55
25	6.5	106	11.2	204	72
26	7.1	103	16.1	250	127
27	5.5	88	6.3	109	15
28	5.8	104	5.2	106	-10
29	7.4	114	11.2	183	52
30	4.1	80	9.0	168	119
Average	6.4	109	9.1	156	45
Cesarean hysterectomy					
1	7.9	103	11.7	170	48
2	8.9	144	11.1	202	24
Average	8.4	124	11.4	186	36

mately the same as that of those who had low cervical sections. There were 7 patients in the low cervical series who exhibited slight decrease in cardiac output. These will receive special comment later.

The cardiac workload is dependent not only on the volume of blood pumped but also on the pressure against which it is expelled. The left ventricular work was calculated according to the formula given by Rose and associates.⁶ Kilogram-meters per minute =
$$\frac{\text{C.O. (L./min.)} \times 1.055 \times (\text{mean B.P.} - 7) \times 13.6}{1,000}$$

The average left ventricular work is increased from 6.7 Kg.-M. per minute before section to 11.8 after section. Therefore, a cesarean section precipitates an increase in left ventricular work amounting to approximately 76 per cent within a matter of minutes. This figure has been reduced to 8.7 Kg.-M. per minute by the seventh postoperative day (Table II). In the 2 patients who had cesarean hysterectomies, the workload increased from 10.8 Kg.-M. per minute before operation to 15.1 immediately after operation (Table III).

Fig. 1 illustrates that the increase in output is accomplished largely through an increase in stroke volume, the heart rate being decreased. The stroke volume immediately after section was 118 c.c. as compared to 74 c.c. prior to section.

The mean blood pressure (Fig. 2) increased from 85 mm. to 98 mm. Hg, and the total peripheral resistance expressed in dynes times seconds per centimeter⁻⁵ decreased from 1,095 to 955. Each has returned toward preoperative levels by the seventh postoperative day.

The only other data of real significance are the alterations in pulmonary blood volume (Table II). The pulmonary or central blood volume increases from 1,642 c.c. before section to 2,058 c.c. after section. This is an absolute increase of approximately 400 c.c. and probably largely represents the volume of blood squeezed from the uterus into the systemic circulation.

Table III lists the average data for the 2

Table II. Average hemodynamic values for 32 patients studied for the effects of low cervical cesarean section

	<i>Before cesarean section</i>	<i>After cesarean section</i>	<i>Seventh day</i>
Cardiac output (L./min.)	6.4	9.1	7.4
Left ventricular work (Kg.-M./min.)	6.7	11.8	8.7
Stroke volume (c.c.)	74	118	106
Blood pressure (mm. Hg)	107/68	125/78	112/72
Mean blood pressure (mm. Hg)	85	98	89
Heart rate (beats per min.)	92	81	75
Circulation time (arm to leg in sec.)	16.6	13.3	14.5
Pulmonary (central) blood volume (c.c.)	1,642	2,058	1,894
Total peripheral resistance (dynes · sec./cm. ⁻⁵)	1,095	955	981

Table III. Average hemodynamic values for 2 patients studied for the effects of cesarean hysterectomy

	<i>Before cesarean section</i>	<i>After cesarean section</i>	<i>Seventh day</i>
Cardiac output (L./min.)	8.4	11.4	8.4
Left ventricular work (Kg.-M./min.)	10.8	15.1	10.3
Stroke volume (c.c.)	95	136	96
Blood pressure (mm. Hg)	123/78	122/80	117/72
Mean blood pressure (mm. Hg)	97	99	92
Heart rate (beats per min.)	89	85	88
Circulation time (arm to leg in sec.)	14.0	14.0	14.0
Pulmonary (central) blood volume (c.c.)	2,882	5,044	2,075
Total peripheral resistance (dynes · sec./cm. ⁻⁵)	937	687	898

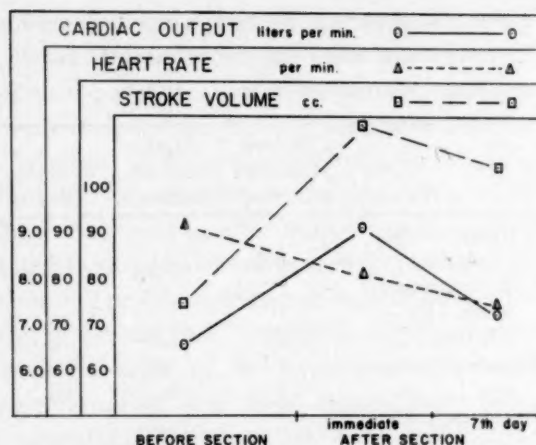


Fig. 1. Graphic illustrations of average values for cardiac output, heart rate and stroke volume before elective section, immediately after section, and on the seventh postoperative day.

patients with cesarean hysterectomies. While it is realized that no conclusions can be drawn from 2 patients, these data are shown to illustrate the striking similarities between these patients and those with low cervical section.

Comment

An analysis of the hemodynamic alterations following cesarean section reveals a close similarity to those data reported previously from patients who were delivered vaginally.³ It was reported that labor produces no sustained increase in cardiac work load but that immediately upon the emptying of the uterus, the cardiac output increases by 19 per cent. The present series of patients who had elective low cervical sections shows that immediately postoperatively the output is increased by 45 per cent. Since in both instances the determinations were done at approximately the same interval post partum, these results should be comparable. It is not likely that cesarean section increases the cardiac output this much more than vaginal delivery. The reason for the apparently greater increase in cardiac output following cesarean section than that following vaginal delivery probably lies in the fact that the control determinations on the former group were done with patients at basal conditions. Many of the control determina-

tions in the vaginal delivery series were done with the patients in early labor exerting varying degrees of physical activity. The control values for the average cardiac output before vaginal delivery (early labor) were 7.2 L. per minute whereas those prior to cesarean section were 6.4 L. per minute. For this reason, it probably would be more accurate to compare postsection values with postdelivery values using presection values as controls in both instances. If one compares the hemodynamic effects of vaginal delivery and cesarean section on this basis it will be found that the results are almost identical. In Fig. 3 the changes in left ventricular work for both vaginal delivery and cesarean sec-

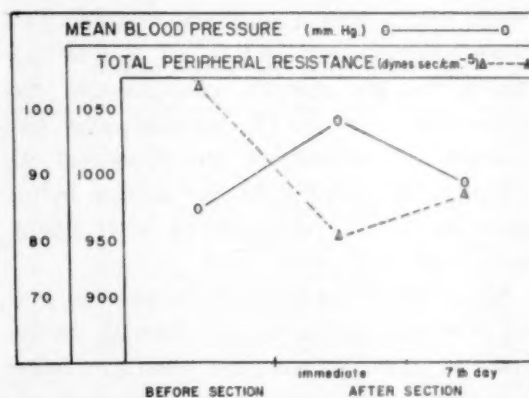


Fig. 2. Mean blood pressure and total peripheral resistance alterations produced by low cervical cesarean section.

tion are shown. These were calculated with the presection values as controls.

The data for the 2 patients who had cesarean hysterectomies show similar changes to those for the low cervical series. It is realized that no definite conclusions can be drawn from the data of 2 patients. However, the cardiac output increase of 36 per cent following cesarean hysterectomy is very similar to the results in the low cervical series.

All available data indicate that emptying the uterus at term is accompanied by drastic alterations in hemodynamics characterized mainly by an increase in cardiac output. It apparently makes little difference how it

is emptied or whether or not the uterus is removed at the time of section. The important fact is that regardless of the manner in which the uterus is emptied it is accompanied by a considerable increase in cardiac work load. The mechanism whereby this occurs is now fairly well understood. As the uterus is emptied a rather sizable volume of blood (approximately 500 to 600 c.c.) is squeezed from the uterine sinuses into the systemic circulation. There is also a release of intra-abdominal pressure. Both of these factors increase the venous return to the heart. This increase in venous return produces a greater diastolic filling, a greater stroke volume, and stronger contraction. Through the Bainbridge reflex an increase in venous pressure produces an increase in heart rate. If one palpates the radial pulse as the uterus is being emptied it will be found to speed up slightly. However, with the increase in cardiac output the increased pressure in the carotid sinus area produces a slowing of the heart rate through vagal action. This reflex will overcome the Bainbridge reflex and within a matter of minutes the radial pulse will be found to be strong, full, and considerably slower than at the time of delivery. The normal heart can compensate for the increased venous return but the weakened myocardium found in patients with heart disease may be unable to increase the volume of blood being pumped and thus decompensation results.

Other evidence that the hemodynamic changes are the result of venous-side altera-

tions is the fact that the increased blood pressure immediately postoperatively is supported by the cardiac output and not the peripheral resistance. The total peripheral resistance, in fact, decreases significantly following either vaginal delivery or cesarean section (Fig. 2).

A closer look at the 7 patients in the low cervical series who exhibited decreases in cardiac output immediately postoperatively is interesting. Four of the 7 showed an increase in heart rate and a decrease in mean blood pressure rather than the reverse as was seen in most cases. The other 3 showed either no significant change in these functions or slight increases in mean blood pressure and decreases in heart rate. With an increasing cardiac output the blood pressure would be expected to increase, being supported by the output. Also, with the output increasing as a result of increased stroke volume, the heart rate would be expected to drop. The picture presented by the 4 mentioned above is that of the effects of excessive blood loss, i.e., a drop in mean blood pressure, increase in heart rate, and decrease in cardiac output. The blood volume determinations in these patients showed decreases following operation amounting to 1,000 c.c. to 2,000 c.c. This is thought to be sufficient to account for the hemodynamic changes found.

The clinical significance of these data lies in the fact that here we have scientific evidence to support the dictum that in patients with heart disease cesarean section should be reserved for obstetric indications. The cardiac work load is just as great following elective cesarean section as it is following labor and vaginal delivery.

Summary

1. Thirty patients who had elective low cervical cesarean sections and 2 who had cesarean hysterectomies were studied to determine the effects of these procedures on the cardiovascular physiology.

2. The cardiac output increased on the average from 6.4 L. per minute prior to cesarean section to 9.1 L. per minute after the section was completed. This was a 45

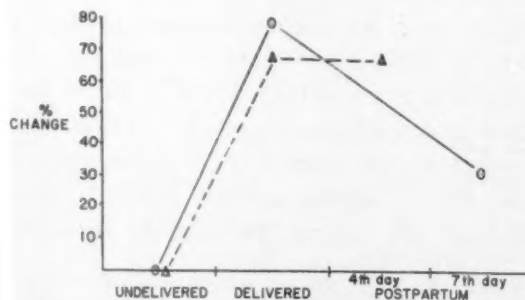


Fig. 3. Graphic illustration of changes in left ventricular work (kilogram meters per minute) following cesarean section and vaginal delivery.

per cent increase. Following cesarean hysterectomy the increase was from 8.4 L. per minute to 11.4 L. per minute or 36 per cent.

3. This increase in cardiac output is reflected in the increase in cardiac work load which was calculated to increase 78 per cent following low cervical section, from 6.7 Kg.-M. per minute to 11.8 Kg.-M. per minute. A similar increase was noted following cesarean hysterectomy and both of these were comparable to the increased work load previously reported following vaginal delivery.

4. Significant increases were also noted in

the stroke volume, mean blood pressure, and pulmonary blood volume.

5. The heart rate and total peripheral resistance were decreased following cesarean section.

6. The observed hemodynamic changes offer scientific evidence that emptying of the uterus produces certain hemodynamic alterations that are largely unavoidable. This is true regardless of the manner in which the uterus is emptied. From the cardiovascular standpoint no one method of delivery has any advantage over another method and cesarean section should be reserved for obstetric indications.

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The problem of prematurity in gravidas with cesarean section scars

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WHEN the obstetrician is consulted by a gravida who has previously undergone a cesarean section, he is likely to have two questions uppermost in his mind. The first relates to whether this patient should be delivered by a repeat cesarean section or by vaginal delivery. The present report will not be concerned with this controversial problem. The second question relates to the timing of a repeat cesarean section in cases in which delivery by the vaginal route has been excluded as a method of management. It is with this aspect of the problem that this report will be concerned.

Materials and methods

The patients reported on were all delivered on the Obstetrical Service of The Johns Hopkins Hospital between Jan. 1, 1950, and Dec. 31, 1958. The study comprises only those women who were delivered of infants weighing 400 grams or more at birth, and is not concerned with pregnancies terminated by abortion. During this period 699 women were delivered of infants of 400 grams or more following one or more previous deliveries by cesarean section. Of these women, 166 had had a single previous classical cesarean section, 216 a single low cervical cesarean section, 16 a single extraperitoneal cesarean section, while 155 women had undergone more than one cesarean section. In 146 cases, the type of cesarean section scar was un-

known. The clinical course of the 699 pregnant women was analyzed for a variety of factors which are presented below in a series of 8 tables and 6 case reports.

Results

From Table I it will be seen that approximately one sixth of the cases were managed by vaginal delivery. In the remaining five sixths a repeat cesarean section was done. In roughly two thirds of the latter cases, the repeat cesarean section was performed prior to the onset of labor. This group has often been referred to as "elective repeat cesarean section." For reasons which will become clear later, it has seemed preferable to use the term "repeat cesarean section prior to labor." In approximately one sixth of the cases, a repeat cesarean section was performed after the onset of labor. Since the diagnosis of labor is not invariably made with certainty, it has seemed desirable to call this group of cesarean sections "repeat cesarean section during presumptive labor."

From Table II it will be seen that the total incidence of premature deliveries (infants weighing less than 2,500 grams) was 15 per cent. When divided into the same categories as those in Table I, the highest incidence of prematurity was found in the vaginal deliveries, followed by the cesarean sections performed in the course of presumptive labor. These figures, which at first sight appear surprising, are subject to adequate explanation.

From this table it is also seen that 8.38 per cent of repeat cesarean sections carried

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Hospital.*

Table I. Method of delivery in 699 cases where patient had had one or more previous cesarean sections

<i>Method and time in relation to labor</i>	<i>Cases</i>	<i>%</i>
Repeat cesarean section prior to labor	465	66.5
Repeat cesarean section during presumptive labor	116	16.6
Vaginal delivery	118	16.9
Total	699	100.0

Table II. Incidence of prematurity following previous cesarean section

<i>Method of delivery</i>	<i>Total deliveries</i>	<i>Premature deliveries</i>	
		<i>No.</i>	<i>%</i>
Repeat cesarean section prior to labor	465	39	8.38
Repeat cesarean section during presumptive labor	116	28	24.1
Vaginal delivery	118	38	32.2
Total	699	105	15.0

out prior to labor yielded infants with birth weights of less than 2,500 grams. Table III deals with this group of women who are often said to have undergone "elective" repeat cesarean section. If the fact be remembered that a woman who has previously undergone a cesarean section is not immune to a variety of obstetrical complications, the term "elective" repeat cesarean section needs further analysis. The term "elective" arose from the fact that the obstetrician "elected" to perform the cesarean section in certain cases of pelvic contraction before labor had demonstrated disproportion. The issues involved in the present problem are quite different. Thus, in 102 of our cases the repeat cesarean section done prior to the onset of labor was forced on the obstetrician by the presence of complications which no longer allowed him to delay the performance of the operation. Therefore the timing was not elective. For this reason the repeat cesarean sections carried out prior to the onset of labor have been separated into (1) the 102

cases in which the presence of toxemia, abruptio placentae, diabetes, placenta previa, premature rupture of the membranes, and miscellaneous other complications, forced the timing of the repeat section; and (2) a separate group in our series, 363 cases, in which a "purely elective" repeat cesarean section was performed. This group comprises the women who were delivered by repeat cesarean section, in which cases the obstetrician, in the absence of any complications affecting the timing of the repeat section, was the sole determiner of the date on which the operation would be performed. It will be noted that the incidence of premature deliveries in this group was 4.7 per cent. In the group in which the timing of the section prior to the onset of labor was influenced by the presence of a complication of pregnancy, the incidence of prematurity was 21.5 per cent; the birth weight of half of these infants was less than 2,000 grams. That this method of subdividing this group of cesarean sections is justifiable is best borne out by the fact that one of these infants at birth weighed 650 grams, the delivery in fact constituting a therapeutic abortion performed on account of poliomyelitis. Such cases can

Table III. Incidence of prematurity in repeat cesarean sections

<i>Timing</i>	<i>Total deliveries</i>	<i>Premature deliveries</i>	
		<i>No.</i>	<i>%</i>
Timing of repeat section forced by complications	102	22*	21.5
Toxemia	47		
Abruptio placentae	3		
Diabetes	20		
Placenta previa	1		
Premature rupture of membranes	22		
Miscellaneous	9		
Purely elective repeat cesarean section	363	17	4.7
Total	465	39	8.38

*Weighing less than 2,000 grams = 11 or 50 per cent of these prematures.

hardly be called "elective" cesarean sections from a timing viewpoint.

We are left then with the fact that, where the estimated duration of gestation was the sole determinant of the timing of a repeat cesarean section, 17 premature deliveries occurred in a total of 363 cases.

In Table IV the fate of these 17 infants is analyzed. From this table it will be seen that only 1 of the 17 infants died, so that the incidence of neonatal death associated with prematurity in 363 "purely elective" repeat cesarean sections was 1 in 363, or 0.28 per cent. This infant weighed 2,435 grams.

The smallest of the 3 premature infants in this group was born to a 30-year-old patient who, in a previous pregnancy, had had toxemia. Throughout the course of the present pregnancy her blood pressure vacillated around levels of 130/88, with the diastolic pressure never rising above 90 or the systolic above 140, so a diagnosis of toxemia could not be made. During the last 2 months various observers noted the fact that there seemed to be no increase in the size of the uterus. A "purely elective" repeat cesarean section was carried out on the two hundred sixty-ninth day of pregnancy, based on menstrual data, when fetal weight was estimated to be 2,400 grams.

The second smallest infant was born to a 31-year-old woman who had an entirely normal prenatal course. An elective repeat cesarean section was carried out 3 days prior to the expected date of confinement. The estimated fetal weight at that time was 2,800 grams. The infant presented by the breech.

The third smallest infant was born to a 32-year-old patient who also had an entirely normal prenatal course. Twelve days prior to the expected date of confinement, with the fetal weight estimated by various observers ranging from 2,800 to 3,400 grams, a "purely elective" repeat cesarean section was carried out. The infant weighed 2,160 grams.

All 3 of these infants did well, although a suspicion of hyaline membrane disease was raised in the second case.

Table V presents an analysis of the cases in which a repeat cesarean section was

Table IV. Weight range of 17 premature infants delivered by elective repeat cesarean section

Weight range (grams)	Total	
	Deliveries	Perinatal deaths
2,499-2,400	9	1
2,399-2,300	5	0
2,299-2,200	0	0
2,199-2,100	1	0
2,099-2,000	1	0
1,999-1,900	0	0
1,899-1,800	1	0
Total	17	1

Table V. Analysis of 28 deliveries of premature infants

	No. of deliveries	Perinatal deaths
<i>Gestational age (days)</i>		
231-240	4	
241-250	5	
251-260	5	
261-270	4	
271-280	3	
More than 280	2	
Unknown	5	
	28	
<i>Weight range (grams)</i>		
2,499-2,000	22	3
1,999-1,500	4	1
1,499-1,000	2	1
999- 400	0	0
	28	5
<i>True labor proved on pelvic examination</i>		
True labor proved on pelvic examination	16	
True labor not proved on pelvic examination	12	
	28	

carried out after the onset of presumptive labor. The incidence of prematurity in this group was 24.1 per cent. At first sight this incidence seems inordinately high. In fact, those who have advocated awaiting the onset of labor prior to the performance of a repeat cesarean section have based their arguments on the dangers inherent in performing this operation prior to that time, and have argued that the onset of labor

was, perhaps, the best criterion for assuring the delivery of term infants. We have carefully analyzed all of these cases to ascertain whether labor really was present. All of the patients thought they were in labor, and on abdominal palpation intermittent hardening of the uterine musculature was felt. In 12 of the 28 patients, however, there was no evidence of labor on vaginal examination, if labor be defined as "progress in the dilatation and/or effacement of the cervix." If we assume that these 12 patients may not have been in labor, we are still left with an incidence of prematurity of 13.8 per cent or 16 of 116 cases. It is to be noted that, in 8 of the 12 cases in which no proof of true labor by vaginal examination was present, the decision to perform the cesarean section was not based solely on the presence of what was thought to be labor but was influenced by complications of pregnancy, 4 being suspected of having dehiscences of the uterine scar. This group of patients produced smaller infants than those delivered by cesarean section after the onset of true labor, proved by vaginal examination.

A second explanation of the high incidence of prematurity in this group may be found under "gestational age" in Table V. From this it is apparent that the onset of presumptive labor occurred considerably earlier in gestation than one would normally expect. If the two hundred eightieth day of gestation be the day on which the onset of labor will most often begin, it must be remembered that the day of onset of labor will be widely distributed around this mark. It is clear from Table V that the patients in this group are predominantly from the very early part of such a distribution curve. They were predominantly women who went into labor earlier than most other women and so did not allow us to set a date for a "purely elective" cesarean section. Therefore, if all of the 363 patients on whom a "purely elective" cesarean section was performed had been allowed to go into labor before the section was carried out, it would have been found that the incidence of prematurity in patients who were operated

Table VI. Analysis of 38 vaginal deliveries of premature infants following previous cesarean section

Weight range (grams)	No. of deliveries	Perinatal deaths
2,499-2,000	18	3
1,999-1,500	10	6 (includes 1 twin)
1,499-1,000	3	3
999-400	6	7 (includes set of triplets, all of whom died)
Unknown	1	0
Total	38	19

upon after true labor had started would have been much smaller.

Table VI analyzes the premature deliveries which occurred by the vaginal route. Again, the high incidence of prematurity in this group, 32.2 per cent, can be explained on the basis of selection: (1) the small size of the infants at the time of the onset of labor and (2) the fact that 10 of the infants had died before labor started.

The decision to perform a repeat cesarean section prior to or after the onset of labor is based on several factors. The advocates of the operation after the onset of labor base their opinion on the danger of delivering premature infants when a "purely elective" cesarean section is performed. The advocates of the "purely elective" repeat cesarean section base their opinion predominantly on two arguments: (1) They feel that cesarean section is an operation to be carried out under optimal circumstances which might not be present in the dead of the night, when hospital facilities are not always functioning at their peak, or shortly after ingestion of a large meal, with the added hazards of anesthesia. (2) They feel also that the scar in the uterus is more likely to give way during labor than prior to it. Therefore, an analysis was made of those cases in which rupture or dehiscence of the uterine scar occurred. Differentiation between rupture and dehiscence is a difference in nomenclature of fairly recent origin. All obstetricians believe that uterine rupture carries more ominous

connotations than dehiscence. For the purposes of this study, dehiscence has been defined as "a separation involving the entire myometrium, but confined to the scar of the previous cesarean section." It involves connective tissue of the previous scar only. Rupture of the cesarean section scar in this study is defined as "a separation involving the entire myometrium, but also involving fresh myometrial tissue. It is, therefore, not entirely restricted to the site of the previous cesarean section scar."

In our series of 699 patients with previous cesarean sections, rupture or dehiscence occurred in 6 cases, or 0.85 per cent (Table VII). Of these, 3 occurred after the onset of labor, and 3 prior to it. When the duration of gestation at the time the scar separated is examined, it is found that a policy of performing cesarean sections 10 days prior to the onset of labor will not of itself guarantee elimination of scar separation or rupture. Moreover, a study of these cases has revealed no trustworthy criteria by which the integrity of a cesarean section scar can be determined.

Case reports

Case 1. The first case in Table VII occurred in a 20-year-old para 2-0-0-1 who had a normal vaginal delivery in 1949. In 1951 she underwent a classical cesarean section for transverse presentation and abruptio placentae with fetal death in utero. On the two hundred sixty-second

day of the present pregnancy while at home she experienced a sudden, lower midline pain in the abdomen which radiated to the shoulder and rectum. The patient fainted. She was brought to the hospital in deep shock. After adequate supportive therapy she was operated on. It was found that the old scar was completely separated and extended 2 cm. medial to the left cornu. Extrusion of the infant had been prevented by an anteriorly situated placenta. A 2,885 gram infant was delivered in poor condition, but was resuscitated and did well. A subtotal abdominal hysterectomy was performed.

Case 2. The second case was that of a 35-year-old para 2-0-1-2 who in 1951 had had a low cervical cesarean section with a Krönig incision which extended to within 3 cm. of the cervix and upward into the fundus of the uterus. The section was performed for prolonged labor, uterine inertia, and contracted pelvis after the membranes had been ruptured for 40 hours and 3 intravenous courses of oxytocin had failed. For several days post partum she had a temperature of 101° to 102° F., believed to be due to endometritis. In 1953, an elective repeat cesarean section was done through the same incision. On the fifth postoperative day her temperature had risen to 102° F. and a diagnosis of endometritis and parametritis was made. On the two hundred sixty-second day of the present pregnancy, the patient had taken 2 doses of milk of magnesia at home. She came to the hospital with lower-midline cramps which were relieved by a bowel movement. Dehiscence of the uterine scar was considered, but there were no other symptoms pointing to it. The estimated fetal weight was 2,600 grams. The patient was feeling fine and was discharged in the morning of the two hundred sixty-third day. She returned that night with rupture of the membranes of 12 hours' duration; the onset of labor came 15 minutes later. She was prepared for a routine repeat cesarean section. When the abdomen was opened, a large hematoma was found to cover the anterior uterine wall, extending to the right pelvic wall and filling the right broad ligament. It extended partially into the left broad ligament also. The entire scar had separated. No additional incision was made in the uterus; a 3,285 gram infant was delivered in fair condition, and did well. On the left lateral wall of the uterus an abrupt break in the myometrium was present to within 2 cm. of the external os. The blood clot along the edge of this separation had reached a de-

Table VII. Analysis of 6 cases of dehiscence or rupture of uterine scar

Previous section	Time of separation	Infant weight (grams)
<i>Rupture</i>		
Classical*	262 days	2,885
Low cervical, Krönig, twice	263 days	3,285
<i>Dehiscence</i>		
Classical	259 days	3,300
Classical	267 days	3,700
Low cervical, Kerr*	256 days	3,225
Low cervical, Kerr + classical*	249 days	2,925

*No labor at time of separation of scar.

gree of organization which suggested that this separation had probably occurred the day prior to operation. A subtotal abdominal hysterectomy was carried out.

Case 3. The third case was that of a 27-year-old para 1-0-0-0 who in 1953 had undergone a classical cesarean section for abruptio placentae with fetal death during labor. On the two hundred fifty-eighth day of the present pregnancy the estimated fetal weight was thought to be 3,300 to 3,500 grams. The patient was admitted for a "purely elective" repeat cesarean section. In the morning of the day of operation she was given a small enema and complained of some low back pain and had some Braxton Hicks contractions. Inspection of the previous cesarean section scar during the operation revealed a marble-sized oval dehiscence in the upper one-third of the previous classical scar which admitted 2 fingers, and which was covered with filmy adhesions. The sides of the dehiscence did not bleed. A 3,700 gram infant in good condition was delivered through the previous cesarean section scar. The uterus was then repaired. This patient has subsequently had a further cesarean section through the same scar which had healed well.

Case 4. The fourth case was that of a 28-year-old para 1-1-0-1 who in 1947 had undergone a normal term vaginal delivery. In 1952 she had a low cervical cesarean section for placenta previa, productive of a 4-pound infant who died neonatally. On the two hundred sixty-seventh day of her present pregnancy the patient was admitted for a "purely elective" repeat cesarean section. On admission she was found to have minimal vaginal spotting, without any other untoward sign or symptom. The estimated fetal weight was 3,200 grams. The elective repeat cesarean section was performed and a 3,225 gram infant was delivered and did well. At the time of the cesarean section a perforation of the previous section scar 2 cm. in diameter and covered by a tiny hematoma was found under the bladder. The scar was repaired in the routine manner.

Case 5. The fifth case was that of a 27-year-old diabetic woman, para 2-0-3-2, who in 1952 and 1954 had 3 early abortions. In 1953 she was delivered by an elective classical cesarean section of a 6 pound, 11 ounce infant with a clubfoot. In 1956, an elective repeat low cervical cesarean section was performed through a Kehr incision. It yielded a 2,925 gram infant with multiple

congenital abnormalities who died. On the two hundred fifty-sixth day of the present pregnancy the patient went into labor spontaneously and without untoward sign or symptom was taken to the operating room for a repeat cesarean section. At the time of operation the low cervical cesarean section scar was found to be separated in its entire length and covered only by serosa. There were some scattered small foci of hemorrhage under it. A 2,925 gram female infant was delivered who did well.

Case 6. The last case was that of a 31-year-old para 2-0-0-2 who in 1955 had undergone a classical cesarean section on the indication of fetal distress. After an entirely uncomplicated prenatal course the patient on the two hundred fifty-ninth day of her present pregnancy presented in the hospital with occasional painless uterine contractions. She soon went into true labor and complained of severe pain in both lower abdominal quadrants. While being prepared for repeat cesarean section a soft suprapubic mass, thought to be the bladder, was observed by the nurse preparing the abdomen. Catheterization yielded no urine. The obstetrician diagnosed dehiscence of the uterine scar, and a cesarean section was performed which yielded a 3,300 gram infant who did well. The entire scar was found to be separated, but the membranes had remained intact. The uterus was repaired in routine fashion.

From these case reports it will be seen that all 6 mothers and infants were discharged alive; and that in only 2 of the 6 cases was a definitive diagnosis of separation of the uterine scar made prior to the operation. It will also be noted that none of the uterine ruptures or dehiscences could have been prevented by the policy of doing a "purely elective" cesarean section 10 days prior to term.

In the light of these data, the desirability of doing repeat cesarean sections prior to the onset of labor must be based on the performance of such operations under optimal conditions. Since infants premature by weight were delivered in 17 of the 363 operations, we thought it worth while to examine whether this incidence of prematurity in "purely elective" cesarean sections could be abolished or diminished. In the vast

Table VIII. Analysis of 17 deliveries of premature infants by purely elective cesarean section

Case No.	Day* first seen	Day† fetal heartbeat first heard	Day‡ cesarean section performed	Birth weight of infant (grams)	
				Actual	Estimated
1	243	243	268	2,160	2,800
2	233	233	259	2,435 (died)	2,800
3	194	194	264	2,475	2,800
4	179	179	277	2,080	2,500
5	165	173	272	2,480	2,700
6	162	162	280	2,450	2,400
7	Not stated	Not stated	283	2,410	2,300
8	Not stated	Not stated	269	1,840	2,400
9	86	Not stated	280	2,390	2,700
10	39	112	"5th month"	2,350	2,600
11	81	165	262	2,340	2,200
12	85	169	279	2,490	2,600
13	121	264	277	2,375	2,500
14	148	148	279	2,425	2,500
15	108	144	274	2,445	2,600
16	72	129	246	2,330	2,650
17	126	126	248	2,435	2,700

*Day of gestation, calculated from first day of last menstrual period on which gravida was first seen in pregnancy.

†Day of gestation, as calculated above, on which the fetal heart was first heard.

‡Day of gestation, as calculated above, on which the section was performed.

majority of instances, the timing of the "purely elective" cesarean section was determined by one person, the Chief of the Service, Dr. Eastman. In setting the time for the purely elective repeat cesarean sections it has been his policy to weigh heavily the time of the first appearance of the fetal heartbeat.

Table VIII is an analysis of the 17 premature infants from this group on the basis of the day of gestation on which the fetal heartbeat was first heard. From this table it will be seen that in the first 6 cases the patient was first seen in our Clinic at a time when one would have expected the fetal heartbeat to be already present, so that this criterion could not help us in determining the duration of the pregnancy.

The onset of the last menstrual period was uncertain in Cases 7 and 8, and the day on which the fetal heartbeat was first heard in Cases 7, 8, and 9. This was due either to unreliability of the patient so far as her last menstrual period was concerned, or to our inability to be certain whether a fetal heartbeat was really present

on a given day, usually because of the obesity of the patient. In these cases the time of the appearance of the fetal heartbeat was of no assistance in dating the pregnancy.

In Case 10 it is obvious that no reliability could be placed on the last menstrual period of the patient since a 2,350 gram infant was delivered by cesarean section carried out in the fifth month, as estimated from the patient's date for her last menstrual period. We are left with 7 cases out of 17 in which the time of first appearance of the fetal heartbeat might have been of assistance. In Cases 11, 12, and 13, it will be noted that the fetal heartbeat was first heard in the twenty-fourth week of pregnancy or later, but in these cases more importance was attached to the first day of the last menstrual period than to the time of the first appearance of the fetal heartbeat. All 3 cesarean sections, performed close to term, were productive of premature infants.

Cases 14 and 15 are representative of cases in which the fetal heartbeat is first heard in the twenty-first week of pregnancy, in which a cesarean section is carried out

close to term, but in which an infant, premature by weight, is delivered. These cases probably represent infants who although premature by weight are at term by gestational age.

Cases 16 and 17 are instructive in that the fetal heartbeat was first heard in the nineteenth week of pregnancy. This seemed to correspond quite well with the last menstrual period given by the patient. Yet, in the subsequent course of pregnancy our feeling was that these patients were one month further along in their pregnancy than the last menstrual period or the first appearance of the fetal heartbeat would suggest. Conse-

quently, more than one month prior to the estimated date of confinement based on the last menstrual period, elective cesarean sections were carried out, and produced infants premature by weight. Therefore, had we followed in all cases our routine of laying great store by the first appearance of the fetal heartbeat, and worked on a basis of assuming that the patients' menstrual data are correct when the fetal heartbeat is first heard approximately 20 weeks after the first day of the last menstrual period, only Cases 14 and 15 could be considered exceptions to a working rule which, in the light of our data, we have had no reason to regret.

Neonatal mortality associated with cesarean section for severe toxemia of pregnancy

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THE effect of analgesia and the various forms of anesthesia on neonatal mortality has to date proved to be extremely controversial. The greatest argument centers around the delivery of premature babies, especially those delivered by cesarean section. Most authors^{1, 2} concur that avoidance of sedation and inhalation anesthesia in the latter is the safest approach to delivery in the average hands. The trend in choice of anesthesia over the past decade has been away from inhalation to local or conduction anesthesia with the avoidance of any premedication other than atropine. However, of equal importance are the ability of the obstetrician to conduct an atraumatic delivery, the adeptness of the anesthesiologist in administering the anesthetic, and a sound approach to resuscitation of the newborn on the part of both individuals.

The material to be presented for analysis has an unusual combination of factors: (1) severe toxemia demanding termination of pregnancy, (2) prematurity wherein the mother is truly excessively sedated, (3) increased hazards of cesarean section, without the benefit of labor, and (4) the possibility of inhalation anesthesia for delivery. Certainly, at a glance, it would appear that the cards were stacked against the fetus and that the fetal mortality under the above aggregation

of circumstances would be significantly greater than normal. We felt that it might be illuminating to determine to what extent, if any, fetal mortality was affected by the type of anesthesia in heavily sedated fetuses obtained from a compromised toxemic environment. At the same time, additional information could be gained on whether cesarean section itself, absence of labor, twin gestation, and eclampsia, would prove to be detrimental. It also affords an excellent opportunity to estimate the hazards of toxemia itself, as to whether there is a "toxic" factor in force, or be it placental compromise, or that survival is dependent primarily on the period of gestation, unrelated to these proposed factors.

Material

The material was accumulated through a 6 year period starting Jan. 1, 1949, and ending Dec. 31, 1954, from the Obstetrical Department of Cook County Hospital, Chicago. During this time a total of 1,421 cesarean sections were performed, of which 850 were primary and 571 repeat. Cesarean section for toxemia represents 19.2 per cent of all sections, and almost one third (32.2 per cent) of primary sections. Incidentally, the occurrence of toxemia at this institution is generally 8.5 per cent.³

Cesarean sections were performed on 274 patients suffering severe toxemia; 286 babies were delivered. There was no attempt to

From the Obstetrical Department of Cook County Hospital.

Table I. Categorization of survival figures of 286 fetuses delivered by cesarean section from 274

Type of anesthesia	Weight not recorded				< 1,000 grams				1,001-1,500 grams			
	Survived		Died*		Survived		Died		Survived		Died	
	Labor	No labor	Labor	No labor	Labor	No labor	Labor	No labor	Labor	No labor	Labor	No labor
Local		1					9		5			1
												+
												2SB
Spinal	1	6					3		6			5
Inhalation		6							3			3
Type not recorded		3					1					1
Total	1	16					13		14			12

*Under "died" all marked SB were antepartum stillbirths, all other were neonatal deaths.

differentiate toxemia into the various types; by clinical and laboratory evidence the patients displayed the features of severe toxemia which required termination of pregnancy. There were 172 primigravidas, 99 multigravidas, and the parity of 3 was uncertain. Twin gestation occurred in 12 patients, 3 of which were associated with eclampsia. Convulsions occurred in 34 patients preoperatively and in 1 case postoperatively. All patients were on energetic therapy and were heavily sedated. Morphine and paraldehyde combination was used frequently; on occasion meperidine and barbiturate were substituted. At delivery, an additional obstetrical resident was present whose sole duty was the immediate newborn care. Gastric aspiration was not generally performed, but liberal use was made of tracheal catheter aspiration of the lower, as well as the upper, respiratory tract. Because of the training programs for obstetrics and for anesthesia, the operation, anesthesia, and care of the newborn were conducted by a multitude of changing personnel. Any good results cannot be attributed to consistency of surgical management.

The cases were divided according to weight groups. Mortality rates were analyzed in reference to the type of anesthesia (local, spinal, inhalation) and whether or not labor preceded cesarean section (Table I). Of the babies, 125 weighed over 2,500 grams, 52 between 2,001 and 2,500 grams, 53 between 1,501 and 2,000 grams, 26 between 1,001 and 1,500 grams, and 13 were 1,000 grams

or under. In 17 instances the babies' weight or type of anesthesia was not recorded.

Results

The perinatal mortality for all fetuses was 13.9 per cent (38 of 286). Five were antepartum stillbirths. The neonatal death rate was 11.7 per cent. The usual perinatal mortality figures reported in most leading centers are comparable to that of 3.8 per cent reported by Nesbitt and Anderson⁴ in fetuses weighing over 1,000 grams. Webster³ at Cook County Hospital reported 1.88 per cent neonatal deaths in 22,699 fetuses of over 1,000 grams. However, when distributed into weight groups, the perinatal (Table II) and neonatal (Table III) death rate for our series is little different from the over-all statistics presented by Nesbitt and Webster. This conclusion is further supported (Table IV) by comparison with the perinatal mortality rates for primary and repeat cesarean sections as reported by Hall and associates⁵ It is readily ascertained that the majority of deaths occurred in fetuses weighing under 1,500 grams both in our series as well as in those delivered under optimal conditions of local anesthesia and avoidance of analgesia in Webster's series.

In Table V the neonatal death rate per weight group is correlated with the type of anesthesia. All 13 babies weighing under 1,000 grams died; all were delivered under local or spinal anesthesia. Of the remaining babies born alive, the survival rates are approximately the same in each weight group

toxemic mothers according to weight group, type of anesthesia, and labor

1,501-2,000 grams				2,001-2,500 grams				> 2,500 grams				Total
Survived		Died		Survived		Died		Survived		Died		
Labor	No labor	Labor	No labor	Labor	No labor	Labor	No labor	Labor	No labor	Labor	No labor	
	17		3		17		1	12	22	1	1SB	
							+					
							1SB					
	15		2		24			15	30		1	
	13		1SB		8		1	11	26			
	1		1					1	5			
	46		7		49		3	39	83	1	2	286

for all of the 3 anesthetics. There is no consistent relationship between survival and the type of anesthesia. Fetuses weighing over 1,500 grams had uniformly good opportunity for survival regardless of the type of anesthesia. Of the inhalation group, there was only 1 neonatal death in 59 cases, and this was in the 2,001 to 2,500 gram weight group. For local anesthesia there were 5 neonatal deaths in 73 babies, 3 in the 1,501 to 2,000 gram weight group; and 1, respectively, for the other 2 higher weight groups. There were 3 deaths in 87 babies associated with spinal anesthesia for delivery, 2 in the 1,501 to 2,000 gram weight group, and 1 in the group weighing over 2,500 grams. Bernstine⁶ feels that most harm to the infant is due to hypoxia from poor administration rather than to the agent, and with general anesthesia, if the administration is good, the infant may be anesthetized but not anoxic. In our series the inhalation group, though containing somewhat fewer cases, surprisingly has the least number of deaths proportionately. At least it can be assumed that inhalation anesthesia is every bit as favorable as local or conduction anesthesia.

Since the neonatal mortality figures are not dictated by the type of anesthesia, we can inspect the cases as to the influence of analgesia. As previously mentioned, all mothers were heavily sedated. Admittedly a large number of fetuses at birth were depressed, but not anoxic, and responded to stimulation and resuscitation. We must emphasize as have others, notably Greenhill⁷

that there is a difference between drug depression and anoxia. In comparing our statistics with those of Webster where the majority (90 per cent) of prematures were delivered "ideally" without sedation and under local anesthesia, the figures are almost identical. This leaves one with the assumption that heavy sedation apparently does not contribute to increased neonatal death.

Convulsions occurred in 34 patients prior to delivery. These included 3 sets of twins. The perinatal mortality of 24.3 per cent as anticipated is relatively high. However, most of these deaths occurred in the markedly premature babies who weighed under 1,500 grams. In the group of babies weighing over 1,500 grams, there were 3 deaths, 1 antepartum stillbirth, and 2 neonatal deaths. These latter 2 babies were delivered under local anesthesia. Here as with severe pre-eclampsia, if the baby is born alive, survival is dependent primarily upon weight and does not appear to be influenced by excessive sedation or type of anesthesia.

In reference to the presence or absence of labor prior to cesarean section, none of the prematures had been in labor. Of babies weighing over 2,500 grams, 85 were not exposed to labor with 1 neonatal death (spinal anesthesia), and in 40 conditioned by labor, there was also 1 neonatal death (from eclampsia). There were no intrapartum deaths in either group. Although the number of cases is limited, there is no material difference in survival rates. The presence or absence of labor apparently is not relevant.

Table II. Perinatal mortality rates—comparison with over-all figures at Johns Hopkins Hospital

Author	Weight (grams)				
	1,000	1,000-1,499	1,500-1,999	2,000-2,499	2,500
Nesbitt and Anderson (26,776 fetuses)	Not recorded	59.1	29.7	8.4	2.0
Our series (286 fetuses)	100	46.2	13.2	5.8	2.4

Table III. Comparison of neonatal death rates in our series with Webster's figures for all of Cook County Hospital

	Weight (grams)							
	1,000		1,000-1,499		1,500-2,499		2,500	
	Webster	This series	Webster	This series	Webster	This series	Webster	This series
No. of live births	225	13	362	26	2406	103	19,931	124
No. of neonatal deaths	208	13	154	12	164	8	106	2
Per cent neonatal deaths	92.44	100	42.54	46.2	6.81	7.8	0.53	1.6

Comment

Diddle and associates^{8,9} in 2 different series were unable to find evidence that cesarean section carries an inherent hazard for the fetus, diminishing its opportunity for survival. Contrary to this is the popular conception that vaginal delivery is safer than abdominal delivery when all conditions are equal. Sullivan and Campbell¹⁰ in analyzing 1,000 cesarean sections make this contention. Hesseltine and Freese¹¹ recently wrote that living term babies delivered by the vaginal canal had a mortality of 0.4 of 1 per cent, whereas the fetal loss in cesarean sections was 0.9 per cent. From this they conclude that the vaginal delivery is twice as safe for the fetus as cesarean section. This is more realistic than Simpson's¹² conclusions that in infants born weighing over 2,000 grams, the neonatal mortality in cesarean section is 8 times that for those delivered by the vaginal route. However, in 1,000 consecutive cesarean sections, Bloxson¹³ had but 2 neonatal deaths. Hess¹⁴ had no fetal deaths in 422 uncomplicated sections. Bryant, in discussion of Diddle's⁸ paper, quoted a 0.5 per cent fetal neonatal death rate in 1,553 repeat cesarean sections. Some have progressed beyond conceding equal survival opportunity for vaginal and abdominal delivery, and

claim the mortality is lower with cesarean section.¹⁵ In this series we found no difference in mortality rates between those with labor and those not exposed to labor prior to delivery. From this and from the range of opinions and figures, it would seem safe to assume that vaginal delivery or labor preceding abdominal delivery has little advantage in fetal survival over direct abdominal delivery in severe toxemia of pregnancy where termination of pregnancy is indicated. This same sentiment is not applicable to maternal morbidity, complications, and mortality and, therefore, we recommend vaginal delivery¹⁶ for maternal rather than fetal reasons.

Many authors^{5, 17-19} have shown that in a mature group of infants there is no difference in the perinatal mortality with the different types of anesthesia. Of these authors, Hellman and Higson,¹⁹ and Hall and co-workers,⁵ have provided evidence that this applies to premature babies as well. Our series offers further support for both categories of babies, in that the perinatal (particularly neonatal) mortality rates for premature and mature babies are not affected by the type of anesthesia. Although there are minor variations among the types of anesthesia, these are not statistically significant.

If they were, they would favor inhalation anesthesia as the one of choice.

Webster,³ in an analysis of factors affecting neonatal mortality at Cook County Hospital, stated that less than 12 per cent of all the patients in premature labor received other than local infiltration; in addition, analgesia was withheld except when warranted by specific maternal indication such as toxemia. In comparing our excessively sedated group with the ideally managed group, the neonatal mortality rates are almost identical, except for the group of babies weighing under 1,000 grams, where we had no survivals and Webster had a 7.56 per cent survival. However, there are only 13 of these cases in our group and an infrequent survival in a continuing series of this category would equate the statistics.

Henderson and associates²⁰ have determined that meperidine hydrochloride in moderate doses prior to cesarean section does not have a deleterious effect on the oxygen saturation of the newborn infant, nor does it

apparently reduce the respiratory response. In their experience it actually decreased the incidence of asphyxia and may even have been beneficial. Fetal blood studies in 29 patients with toxemia of pregnancy by Prystowsky²¹ revealed all oxygen capacity levels to be within the limits considered representative of normal. Evidence, therefore, leads us to believe that babies in cases of severe toxemia, although heavily sedated and anesthetized, are not anoxic. They may be depressed by drugs and inhalation anesthetics but, as Greenhill maintains, "drug depression" independent of anoxia is of limited duration. Our study tends to bear this out.

The survival rates of heavily sedated and anesthetized fetuses in a severely toxemic environment delivered by cesarean section in our series are comparable to those of fetuses delivered under ideal conditions. This can probably be attributed to proper management and resuscitation of the newborn. Modern techniques of combating drug de-

Table IV. Comparison of perinatal mortality rate of 286 fetuses obtained from severe toxemia terminated by cesarean section with 2,219 other primary and 1,597 repeat sections

	Weight (grams)														
	1,000			1,001-1,500			1,501-2,000			2,001-2,500			2,500		
	No. delivered	No. died	% died	No. delivered	No. died	% died	No. delivered	No. died	% died	No. delivered	No. died	% died	No. delivered	No. died	% died
Our series	13	13	100	26	12	46.2	53	7	13.2	52	3	5.8	125	3	2.4
Hall and co-workers ⁵ (2,219 primary)	36	33	91.7	65	24	36.9	126	43	34.1	220	25	11.9	1762	64	3.6
1,597 repeat	4	4	100	10	5	50	24	8	33.3	144	13	9.0	1411	13	0.9

Table V. Type of anesthesia correlated with the neonatal death rate per weight group

Type of anesthesia	Weight (grams)														
	1,000			1,000-1,500			1,501-2,000			2,001-2,500			> 2,500		
	Born	Died	% died	Born	Died	% died	Born	Died	% died	Born	Died	% died	Born	Died	% died
Local	9	9	100	6	1	16.6	20	3	15.0	18	1	5.6	35	1	2.8
Spinal	3	3	100	11	5	45.5	17	2	11.8	24	0	0	46	1	2.2
Inhalation	0	0	0	6	3	50.0	13	0	0	9	1	11.1	37	0	0
Average for weight groups	12	12	100	24	10	41.7	52	6	11.5	51	2	3.9	114	2	1.8

pression and, more important, the establishment of a free airway, are the foremost features in resuscitation of the newborn. At Cook County Hospital, liberal use of the tracheal catheter is probably the most significant factor in fetal revival and survival.

Summary

1. In a comparison of the fetal survival rates of severe toxemia terminated by cesarean section with the statistics at large, the following factors are not influential: (a) type of anesthesia, (b) degree of sedation, and (c) whether or not labor preceded abdominal delivery.

2. Toxemia does not seem to possess a "toxic" element which will influence or compromise neonatal survival rates to any measurable degree, except in so far as to increase the prematurity rate.

3. Fetal survival after delivery in toxemia is dependent primarily on maturity; weight of less than 1,500 grams offers a poor prognosis, that of over 1,500 grams a good prognosis, with detectable improvement with each 500 gram increment.

4. Proper management of the newborn with adeptness at fetal resuscitation is more important than the type of anesthesia and the degree of analgesia.

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A modified technique for cesarean section

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DIFFICULTIES in extracting the fetus by transverse cesarean section in the lower uterine segment are commonly met with in cases of neglected transverse presentation. Some obstetricians resort to the classical cesarean section in such cases. When the uterine cavity is infected, however, the classical cesarean section is ill advised, and for this reason Eastman¹ has suggested that classical cesarean sections be followed by hysterectomy in multiparas with this condition. Difficulties are also encountered during extraction of the fetus in transverse cesarean sections in cases of vertex presentation when the head is large or when it is impacted in the pelvis. These difficulties can cause extension of the uterine incision and lacerations of the uterine vessels,²⁻⁴ as well as trauma to the fetus.

The modification I would like to propose is intended to obviate these dangers to the mother and infant. It has the advantages of the classical section and at the same time peritonization is as easy as for the low flap section.

Description of the modification

We make a small transverse incision in the lower segment near the midline. The wound is extended toward the sides by spreading with two fingers. Then with the scissors we prolong one of the ends of the incision upward toward the insertion of the round ligament. The transverse part of the incision is one-third to one-half shorter than the usual low flap incision. In this way we

avoid severing the uterine vessels. The shortness of the transverse incision enables us to make it low in the lower uterine segment, which facilitates extraction of the head impacted at the inlet. Only a little of the vertical arm of the incision reaches the corpus. It is important to make the transition between the transverse arm and the vertical one somewhat gradual, so that the whole incision line will form a curve. The semicircular incision allows for a longer primary uterine wound than that of the usual low flap cesarean section. In cases of unintentional extension during extraction of the fetus, the semicircular incision involves less vascular areas than does the transverse operation.

The vertical segment of the incision has to be performed sharply, not with the fingers, as the uterine fibers have a tendency to horizontal separation in this region. The semicircular cesarean incision should be performed primarily, not deferred until difficulties in extracting the fetus are encountered in the course of a conventional low flap section.

Analysis of 34 cases

To assess the merit of the proposed modification, a group of 34 such cesarean sections will be compared with 135 low flap transverse cesarean sections. These 169 cesarean sections were all performed at the Department of Obstetrics, Town Hospital, Lowicz, between March 1, 1957, and March 3, 1960. The group of semicircular cesarean sections did not consist of selected cases. In these 169 cases, there were 3 stillbirths (2 fetuses were dead before operation), 7 neonatal

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deaths, and no maternal deaths. All cesarean sections were performed under ether anesthesia.

1. Extraction of the fetus. All together there were 17 cases in which the operative note mentioned difficulty in extracting the fetus or spontaneous extension of the wound. This problem arose in 16 of the 135 low flap transverse operations and once in the 34 semicircular operations. This latter patient had a tonic uterine contraction. These data conform with the observations made during the operation, demonstrating the fact that extraction of the fetus is easier from the semicircular incision. This is especially true in cases of transverse lie and cases in which the fetal head is impacted in the inlet. This is evident from comparison of the group of 21 semicircular cesarean sections to 44 low flap operations in such cases.

2. Blood loss. This was estimated by weighing the surgical linen and was considered excessive if it amounted to more than 1,200 c.c. Cases described in the previous paragraph are not considered here. Eleven cases of excessive blood loss were noted in the group with transverse incisions and one case in the group with semicircular incisions (Patient Z. Z., who received a 250 c.c. transfusion). Unfortunately, our impressions in the operating room were not as optimistic as these figures would indicate. The bleeding, encountered from the transverse incision, may be scanty (about 400 c.c.) or, rarely, abundant (over 1,200 c.c.). This range in the quantity of blood loss is distinctly narrower in semicircular sections for abundant or scanty bleeding is rarely noted. More often the blood loss amounts to about 600 c.c. in these cases. There is, therefore, no notable difference in the *average* amount of blood lost at the two types of operation.

3. Operative morbidity. Analysis shows that there were 102 days on which the patient's temperature exceeded 38° C. for the 135 transverse operations and 40 such days for the 34 semicircular operations. But during the time when the semicircular operations were more often performed, there was an epidemic of influenza. It is therefore felt

that there was no significant difference in the postoperative morbidity in the two groups.

4. Repeated cesarean sections. The semicircular incision has been used in 3 cases of repeated operations. In one case, the operation was performed extraperitoneally. Unfortunately, we can draw no conclusions from so few cases. Corbet⁵ has stated that "eventual side ruptures of the uterus are dangerous." We believe the rupturing of scars is more dependent on the technique of the operator than on the method of operation.

It should be emphasized that the group of 34 semicircular cesarean sections, in spite of the fact that it did not consist of selected cases, includes a proportionately higher number of cases with large (over 4,000 grams) fetuses (11 of 34 and 24 of 135) and transverse presentation (10 of 34 to 20 of 135) in comparison to the low flap operations.

Difficulty in extracting the fetus is met particularly often in cases of neglected transverse lie. The semicircular section permits one to avoid version (which is traumatic to the fetus), because the upper part of the vertical arm lies above the fetal head.

Conclusions

1. Semicircular cesarean sections are superior to transverse cesarean sections in the lower segment: (a) in cases of transverse fetal lie (particularly if neglected); (b) when a large fetal head is strongly impacted in the inlet; (c) in some cases of placenta previa, uterine varices, and repeat cesarean sections.

2. Semicircular incision prevents unintentional extension of the uterine wound.

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Extraperitoneal cesarean section

A simplified technique

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A MATERNAL death recently occurred in our department from generalized peritonitis and septicemia. The patient was a 16-year-old primigravida with pre-eclampsia and cephalopelvic disproportion, whose pregnancy was terminated by transperitoneal cesarean section 38 hours after the membranes had ruptured. This case was presented at our staff conference. One conclusion of the discussion was that the patient might have been offered a better chance for survival had an extraperitoneal cesarean section been performed. Study of existing procedures for the extraperitoneal cesarean section and their related problems resulted in the development of the technique described in this paper.

The concept is erroneous that there is no longer an indication for extraperitoneal section because of earlier intervention in problem cases and the safety factor afforded by antibiotic therapy. Physicians must keep in mind that virulent bacteria may invade the uterus and that the introduction of these organisms into the tissues and the peritoneal cavity by transperitoneal section may spell disaster. Every obstetrician should be able to perform an extraperitoneal cesarean section to be considered a well-rounded practitioner of the specialty.

The modern education program of the obstetrical resident, in addition to didactic

teaching, includes breech extractions, versions and extractions, all types of forceps operations, and cesarean sections, including classical and low cervical, and cesarean section combined with hysterectomy. It should also include a form of extraperitoneal cesarean section.

Experiments at the extraperitoneal approach have been made as far back as 1821 when Ritgen¹ tried it on a patient at the University of Giessen.

Latzko² devised a paravesical technique in 1908 with which he achieved moderate success. Other obstetricians of this era employing his method reported bladder and ureteral injuries, and it was gradually abandoned.

It was not until 1940, when Waters³ developed the supravescical approach, that the operation attained a degree of popularity. His technique was found to be difficult for the average obstetrical surgeon, and repeated performances of this method in various clinics resulted in equivocal appraisal. At this time antibiotic medication came into general use. Many obstetricians abandoned the extraperitoneal operation, rationalizing that the transperitoneal approach for the patient safeguarded by antibiotic therapy was sufficient, even in the presence of infection.

In 1946, Norton⁴ devised the unilateral paravesical approach to the lower segment. Because this operation seemed easier and less time-consuming, interest in it was renewed.

Bourgeois and Phaneuf⁵ in 1949 reported

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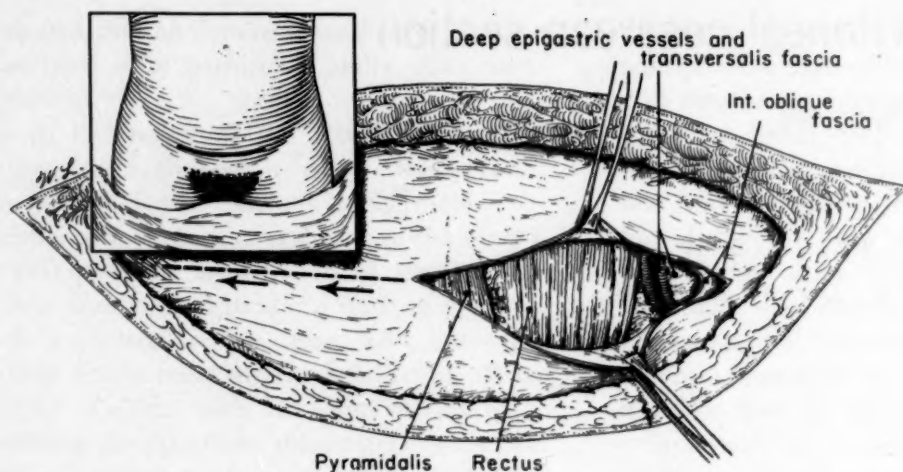


Fig. 1. The skin and superficial fascia are open. The anterior rectus sheath is partially open, and the rectus and pyramidalis muscles are seen. The close relation of the epigastric vessels can be noted. *Inset*, the approximate level of the incision.

a bilateral parasupravesical approach whereby both paravesical spaces were opened; the dissection started down the posterior surface of the bladder and ended, upward, by removal of the peritoneal fold from the anterior surface.

In 1942 at our hospital, the members of the department staff began doing the supravvesical operation as described by Waters. Our results were anything but uniform. With optimum conditions, the operation was excellent and the approach to the lower segment provided all the room desired; but with adverse conditions, the operation was difficult and, on occasion, the bladder and peritoneum were incised.

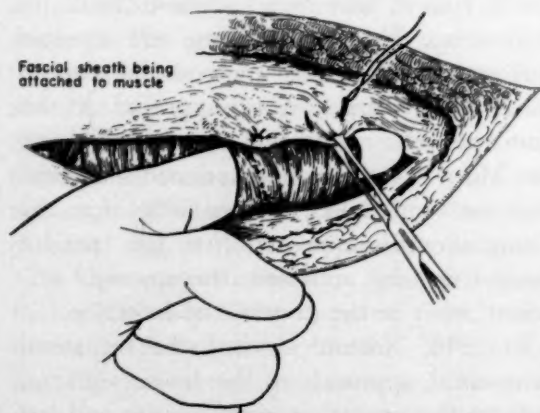


Fig. 2. The rectus muscles have been exposed and elevated by blunt dissection. The method of anchoring the muscle to the fascia is seen. Again the relation of the epigastric vessels can be noted.

After Norton reported his method, our department staff⁶ adopted the paravesical technique. The results were uniformly better. Although the method was easier for the average operator, the exposure afforded was never satisfactory. The large infant and the one in abnormal presentation were hard to deliver through the available space. With use of the vertical S-shaped incision in the lower segment as advocated by Norton, extensions occasionally occurred which were difficult to repair. In institutions where staff members are adept at the extraperitoneal approach, there should be no reason for sacrificing a uterus following cesarean section because of infection. Waters⁷ states, "We have done no cesarean hysterectomies in the last twenty-five years as a treatment for uterine infection. It is our past and present opinion that none should be done."

The purpose of this paper is to present a preliminary report on a new technique for performing the extraperitoneal cesarean section. This operation combines the simplicity of the paravesical operation and the ample room of the supravvesical, while eliminating the difficult dissection of the older supravvesical technique.

Technique

1. The patient is hydrated with 2,000 to 3,000 ml. of 5 per cent dextrose in distilled

water, given over a 2 to 3 hour period. This fluid aids to make the tissues "wet" and to facilitate the dissection. If the patient has edema, this step is not necessary.

2. A Foley catheter is inserted into the bladder and connected to a "Y" tube which is hooked up to a reservoir of sterile water. A tube from the remaining end of the "Y" is placed in a drain basin. By means of this arrangement the bladder may be filled or emptied by clamping or unclamping the proper tubing.

3. The patient is given spinal or peridural anesthesia. The advantages in the use of block anesthesia are: (1) adequate time is allowed for performance of the dissection, and (2) injurious effects of anesthetic agents to the fetus are avoided.

4. A low transverse incision is made in the abdomen. The rectus sheath is transversely incised, and the resulting retraction exposes both rectus muscles (Fig. 1). The index finger is inserted under one muscle from the medial to the lateral aspect, with care being exercised to avoid injury to the deep epigastric vessels. Two Allis clamps are placed on the upper margin of the retracted rectus sheath. While the assistant makes downward traction, 2 sutures are placed lateral to each other and tied so as to anchor the muscle to the sheath (Fig. 2). The clamps are then placed on the lower margin of the sheath and, while the fascia is pulled upward, 2 additional sutures are placed as before. The rectus muscle is transected while tension is applied from underneath by the operator's index finger (Fig. 3). The 4 sutures function to control bleeding from vessels in the muscle and to facilitate muscle approximation when the fascia is being closed. The same maneuver is effected on the opposite rectus muscle. The muscles will retract, enhanced by blunt dissection, providing considerable room.

5. The deep epigastric vessels at the lateral edge of each rectus muscle are isolated, clamped, cut, and ligated. This should be done as inferiorly as possible, allowing the vessels to retract laterally at a later stage without the danger of tearing them. Occa-

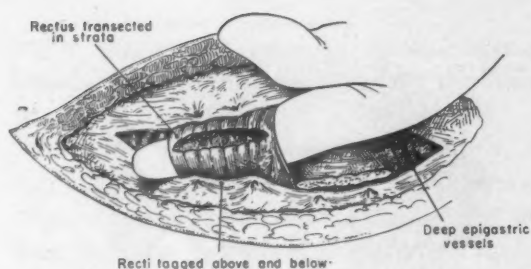


Fig. 3. Both rectus muscles have been anchored to the fascia superiorly and inferiorly, and the left rectus muscle has been transected. It is to be noted here that the muscles are transected in layers rather than from side to side. It is at this point that the relation of the epigastric vessels is of paramount importance.

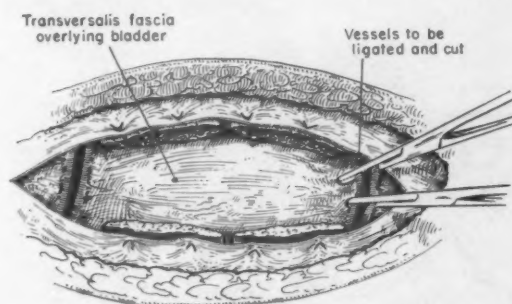


Fig. 4. The muscles are transected and the underlying transversalis fascia exposed. The inferior epigastric vessels are being clamped.

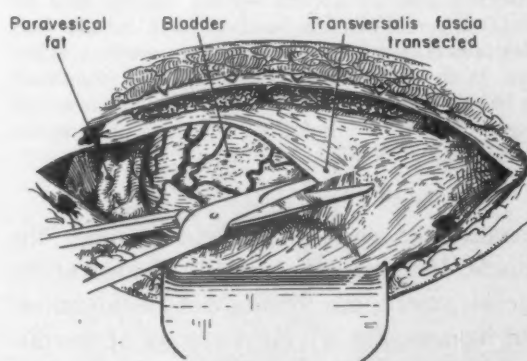


Fig. 5. The transversalis fascia over the bladder is incised. This is done with the scissors beginning in the midline and extending laterally to both sides. The paravesical space on the right is visualized, and the bladder is seen to herniate up through the opening in the fascia. Bladder vessels are also seen, as are the ligated ends of the epigastric vessels. The Balfour retractor blade is in place.

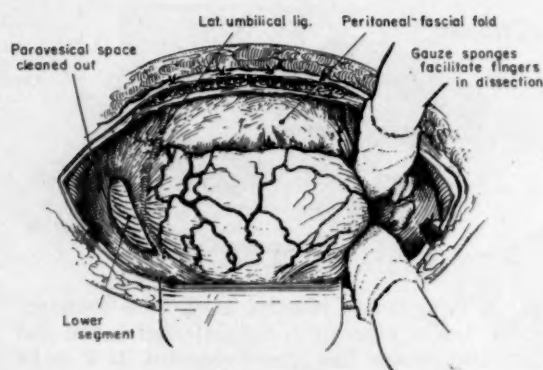


Fig. 6. Blunt dissection with gauze over the fingers is being carried out on the left side. The right side has already been dissected and the lower segment can be visualized. The lateral umbilical ligaments can also be seen. The peritoneal-fascial fold is seen superior to and partially overlying the bladder.

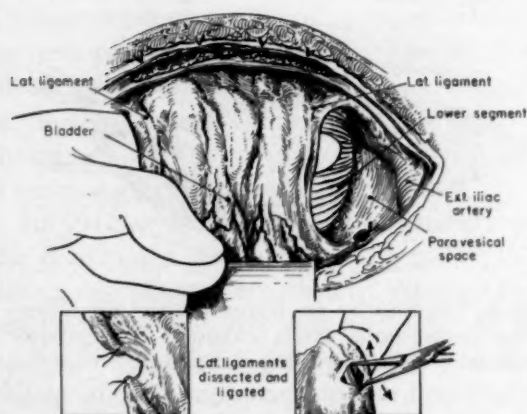


Fig. 7. The two paravesical spaces have been dissected and connected behind the bladder by blunt finger dissection as described in the text. The lateral umbilical ligaments are seen on either side. With a finger behind the bladder, the tissue to be dissected off the bladder now lies over the finger. *Insets*, the isolation, ligation, and section of the lateral umbilical ligaments.

sionally, the vessels are located under the muscle. If the muscle is slowly divided at the lateral aspect, the vessels can be identified and ligated (Fig. 4). At this stage of the dissection there is accessibility to the bladder superiorly and laterally, and the space may be enlarged by placing the lower blade of the Balfour retractor in the inferior border of the incision.

6. The bladder is easily identified after filling with about 150 to 200 ml. of fluid. The transversalis fascia over the bladder is

picked up with tissue forceps, and with the dissecting scissors an incision is made beginning at the midline and extending laterally to both sides (Fig. 5). The transversalis fascia may be variable in different patients, ranging from a structure well defined with a thin layer of fat between it and the bladder adventitia to a structure poorly defined and filmy. The partially inflated bladder will "balloon" upward into the line of incision and the proper plane is attained when the bladder vessels are exposed (Fig. 5).

7. The paravesical spaces are now identified on either side. These are the "yellow chicken fat" areas described by Norton.⁴ They are located lateral to the bladder, medial to the deep epigastric vessels, and inferior to the peritoneal-fascial fold, which is not identifiable at this time.

With a moist 4 by 4 inch gauze sponge on each index finger, the operator incises one paravesical space by blunt dissection down to and exposing about 1 to 2 sq. cm. of the lower uterine segment. The level of dissection should be inferior enough so that the peritoneum is not entered (Fig. 6). An identical procedure is carried out on the opposite side.

8. The index finger is now introduced into one paravesical fossa and tunneled across to the opposite side, with care being exercised not to enter the peritoneum. It is at this part of the procedure where most failures to stay extraperitoneally occur. This hazard can be avoided by directing the finger downward so that it comes across the posterior surface of the bladder and below the peritoneal fold. It is important not to use force, but only gentle blunt dissection. The finger will find the proper plane and can be brought through to the opposite fossa. Occasionally, in repeat sections a plane cannot be found. One should not persist beyond establishing a tunnel on either side which will allow the index finger to exert upward pressure from underneath the bladder. When the finger is in the proper plane, it will be against the lower uterine segment, the bladder will be anterior, and the peritoneal-fascial fold will be superior.

9. It will be noted that thick bands of tissue seem to be holding the peritoneal fold to the bladder on each side. These consist of fat, areolar tissue, and the obliterated hypogastric arteries or lateral umbilical ligaments. The latter go from the hypogastric arteries to the umbilicus passing lateral to the bladder. These obliterated vessels are isolated by blunt dissection down near the bladder, ligated, and cut (Fig. 7). Initially, these ligaments may be mistaken for ureters, but further dissection will make it apparent that this is not the case. As the lateral ligaments are cut, there is a feeling as though "something gave" and the peritoneal fold seems to separate partially from the bladder.

10. The finger is reintroduced into the tunnel and upward traction is made under the bladder and peritoneal-fascial fold. Only areolar tissue holds the fold to the bladder. Starting well below the level of peritoneal reflection, sharp dissection is begun with a scalpel over the anterior surface of the bladder. The tissue to be cut will stand out as small fibrous bands. The finger exerting pressure from underneath the bladder will feel the fold being released (Fig. 8). If the bladder muscularis is exposed, one must seek a more superficial plane, superior to the previous dissection. Eventually, the white line of the peritoneal reflection is identified resembling a hernial sac. Dissection is then carried out about 1 to 2 mm. inferior to the white line. As one pulls upward, the fold will be felt to give and peel off the bladder. Bleeding vessels are clamped as they are encountered.

The width of the fold decreases as the urachus is approached in the midline (Fig. 9). This structure is tied and cut and the dissection is continued down the posterior surface of the bladder until the entire fold is separated. The bleeders on the surface of the bladder are now tied.

The bladder is emptied, a tape placed over it, and the lower blade of the Balfour retractor reinserted, displacing the bladder under the symphysis. Another wide retractor is placed at the upper end of the incision holding up the peritoneal-fascial fold. The whole

lower segment is now in view. There is usually a thin film of fascia over the lower segment which is divided with a scalpel.

11. The uterus is incised transversely. At this stage, a suture is placed in the inferior edge of the incised lower segment and left long because the lower edge tends to fall well down behind the bladder (Fig. 10). The transverse incision is extended by lateral pressure with the fingers. The infant is delivered. Indicated cultures, if desired, are taken at this point. The oxytocic is given

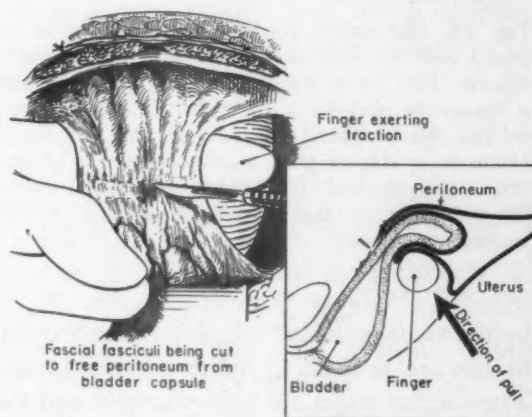


Fig. 8. Sharp dissection of the peritoneal-fascial fold is shown in progress. It should be noted that the width of the fold has decreased after section of the lateral ligaments. Inset, a schematic diagram in sagittal section. It shows the peritoneal fold to be dissected off the bladder, and the direction of pull of the finger behind the bladder. The knife edge is shown cutting the fibrous connective tissue holding the fold to the bladder.

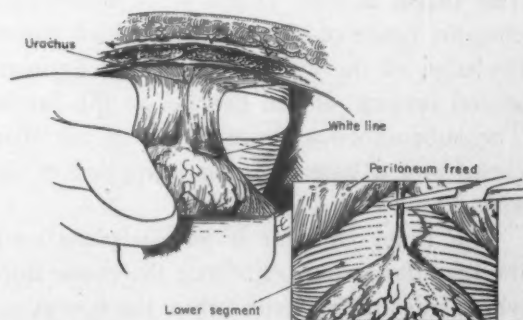


Fig. 9. The dissection is shown near completion as the urachus comes into view. By this time the white line of the peritoneal reflection can be seen. Inset, the dissection completed and the urachus being clamped. Note the ties on the bladder vessels.

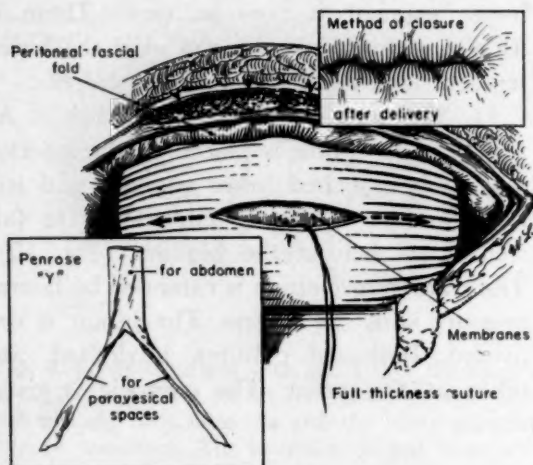


Fig. 10. The entire lower uterine segment is exposed and the line of incision into the uterus is shown. The lower segment is being tagged with a suture to prevent it from falling out of reach behind the bladder. *Upper inset*, the uterine incision after closure with a Lembert suture. *Lower inset*, the method of cutting the conventional Penrose drain so that it may be placed in both paravesical spaces.

by the anesthetist and the placenta and membranes are allowed to deliver spontaneously. The uterine edges are then clamped and the uterus is closed with a double layer of suture in the manner of a low cervical section. After all bleeding has been controlled, the bladder is filled and inspected for injury and additional bleeding vessels.

12. A Y-shaped Penrose drain is now placed with one side of the "Y" in either paravesical area. The peritoneal-fascial fold is allowed to fall back into place (Fig. 10). The fascia is now closed with interrupted chromic figure-of-eight sutures, which causes the edge of the cut muscles to be approximated because of the fixation to the fascia. The subcutaneous tissue and skin are then closed and a large dressing is applied to absorb drainage.

The Foley catheter is left in place until the next day to help eliminate the excess fluid which was administered before the operation. After removal of the catheter, the bladder is tested for residual urine at the next voiding. The drain is removed after 24 hours and the wound redressed. Care is otherwise no different from that after other cesarean sections.

Midline approach. In the presence of a midline scar, the described method of entry is not used, to avoid multiple abdominal scars. Instead, the midline approach is used, and the rectus muscles are retracted laterally rather than transected. The remainder of the operation follows the procedures as listed. The only real disadvantage in this modification is slight loss of exposure.

Analysis of cases

To date, 17 cases have been performed by this method. The series is too small to warrant a critical analysis. Thirteen primary and 4 repeat sections were performed. In one case, failure of the technique necessitated completing the operation as a lower segment transperitoneal section. In the early cases, when the technique was being perfected, the peritoneum was incised five times. When this complication occurred, the opening was repaired and the operation continued as described. The bladder was not entered in any of the cases, and in one case repeated catheterizations were needed for residual urine. In this case the abdomen had to be reopened the first postoperative day and a hematoma under the rectus muscles evacuated.

One patient who was in labor more than 30 hours with ruptured membranes developed a wound infection. Another patient had a seropurulent discharge from the wound for 2 weeks postoperatively.

Thirteen operations were done with use of spinal anesthesia; 2 with epidural; one with general anesthesia with thiopental, ethylene, and d-tubocurarine; and one with no anesthesia. In the latter case, the patient had a transection of the spinal cord at the level of T-9 as a result of a bullet lodged in the spinal cord.

In the series there was one neonatal death which was not attributable to the type of section.

Comment

The type of extraperitoneal cesarean section presented in this report has several advantages. The simplified technique can be

performed by the average obstetrician and requires only one assistant. It provides the operator with sufficient space for delivering large babies or babies with abnormal presentations without the danger of injuring the urinary system, particularly the ureters. It eliminates the difficulties in the dissection around the bladder encountered in the suprav vesical section.

Fifteen to 30 minutes is required to deliver the infant. While the time factor may be considered a disadvantage, there were no untoward effects in any of the infants. The employment of block anesthesia decreases the importance of the time factor with regard to fetal morbidity and mortality as compared to other anesthesia modality. The total time

of the operation does not exceed the average low cervical section by more than 5 to 10 minutes.

Summary

1. The use of extraperitoneal cesarean section in modern obstetrics is discussed and a brief history of the operation is given.

2. A modified technique is described in detail.

3. This technique lessens many of the dangers and difficulties of the old suprav vesical and paravesical approaches.

4. Extraperitoneal cesarean sections can eliminate the necessity for doing cesarean sections combined with hysterectomies in infected cases.

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CURRENT OPINION

Clinical problems

Endometriosis

Case presentation

Miss D. C., 42 years of age, a divorced gravida i, para 0, who had had 1 abortion, was admitted to the hospital because of a sudden onset of cramping abdominal pain. The pain began on the day of admission, first in the left lower quadrant and then spreading to the right lower quadrant. It was accompanied by shoulder pain. The discomfort was accentuated by deep breathing. The patient experienced chills and nausea but no vomiting. There was no change in bowel habits and there were no urinary symptoms. Her last menses, 15 days prior to admission, was normal in all respects. Her previous menstrual period had been normal, 4 weeks prior to the last period. Intermenstrual spotting had occurred at intervals during the previous 4 years. There was no history of dysmenorrhea.

Past history. The patient had had two similar episodes of pain in the last two years. A medical survey had been conducted 16 months prior to this admission because of the pain. The findings were normal. Previous operations consisted of a curettage in 1956 and another in 1959 for intermenstrual bleeding. The diagnosis on each occasion was dysfunctional bleeding and uterine myomas.

Physical examination. The patient's weight was 119 pounds, her height 5 feet, 1 inch. The temperature was 99° F.; the blood pressure 112/68; pulse 70 per minute; and respirations 20 per minute. She was a well-developed, well-nourished woman who appeared younger than her stated age. She was resting quietly in bed. The abdomen was symmetrical and slightly distended. There

was no rigidity but voluntary guarding was present. She was tender throughout the abdomen, particularly in both lower quadrants. No masses were palpable abdominally. Bowel sounds were present in the right lower quadrant, but absent in the other quadrants.

The vulva and vagina were normal. The cervix was normal, but motion of the cervix caused acute pain. The uterus was anterior, two times normal size, irregular, and limited in motion. There was fullness and tenderness in the region of the adnexa, especially on the left. The posterior cul-de-sac contained a tender nodule.

Laboratory tests and results. The hemoglobin level was 14.7 Gm. per cent and the hematocrit determination 45 per cent. The white blood count was 11,350 with 13 per cent band forms, 76 per cent segmented polymorphonuclear leukocytes, 9 per cent lymphocytes, and 2 per cent monocytes. The sedimentation rate was 17 mm. per hour. The urine was normal, the specific gravity 1.031. A second leukocyte count 14 hours after the first count was 6,540 with a normal differential. The hemoglobin level at this time was 13.5 Gm. and the hematocrit determination 43 per cent.

Diagnosis. The diagnosis was made of endometriosis with recurrent intraperitoneal bleeding and uterine fibroids.

The patient volunteered the information that she was planning to get married shortly and that she would like to retain her child-bearing function.

Operative findings. In the abdomen there was a large amount of dark brown stained

peritoneal fluid. The pelvic peritoneum was studded with multiple brown hemorrhagic spots. There were multiple pelvic adhesions. The uterus was enlarged to one and one-half times normal size and contained multiple subserous myomas. The left tube was adherent, club shaped, and dilated, and the fimbria were sealed. The left ovary was adherent but normal. The right tube was normal and patent to retrograde injection of air. The right ovary was adherent and contained a "chocolate cyst" measuring 4 by 6 cm. in diameter. There were multiple endometrial implants on the pelvic organs and the parietal peritoneum.

Problem: Discuss (1) the operative procedure you would perform in this particular patient and (2) the management of endometriosis in general.

Consultation

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Medical School

The case presented has many interesting facets, psychological and sociological as well as clinicopathological.

The patient's past history of two previous episodes with normal findings, including those on curettage in 1956 and 1959, contribute little to the acute episode resulting in the admission under discussion.

The vital signs, temperature, pulse, blood pressure, and respiration combined with laboratory and physical findings point to intraperitoneal hemorrhage with either coincidental or contributory endometriosis.

Bleeding into the peritoneal cavity from endometrial cysts without the association of pregnancy has been a rarely diagnosed clinical entity on either the clinical or private services under my observation. In the absence of ectopic gestation, symptoms assigned to free bleeding within the peritoneal cavity are diagnosed and recorded, without proof, as bleeding from the corpus luteum and occur most frequently in the postovulation

period. This picture is compatible. These diagnoses most often are of necessity presumptive, and the need for surgical intervention or minor surgical diagnostic procedures, i.e., culdocentesis, culdoscopy, or colpotomy, is rarely indicated. Culdocentesis and/or colpotomy are the procedures of choice if the condition of the patient requires something other than observation and supportive measures. The presence of palpable cul-de-sac endometriosis indicates caution in penetration of posterior cul-de-sac due to the frequency with which the anterior wall of the rectosigmoid is fixed to the contiguous cul-de-sac peritoneum.

The preoperative diagnosis of endometriosis (tender nodule in the posterior cul-de-sac) and uterine myomas with history of recurring mild extraperitoneal bleeding episodes is easily concurred with. However, considering the episodes of intraperitoneal bleeding with the combined clinical picture, symptoms, and laboratory and physical findings in full, I do not feel that laparotomy was justified.

Be that as it may, finding oneself at laparotomy and confronted with the findings described, bilateral partial oophorectomy would be done with resection or fulguration of significant implants. Myomectomy would not be done unless the myomas were over 4 cm. in diameter, and the closed tube would be opened by simple salpingostomy if aspiration revealed a nonpurulent content. Early marriage would be recommended with pregnancy its immediate goal.

I must digress and revert back to the point that there is serious doubt an emergency state existed indicating operation before a critical evaluation was made of the intent to marry and the desire to have children. When convinced of their mutual interest and the male fertility status approved, the risk of recurrence of both the endometriosis and myoma following operation would be thoroughly discussed. After tubal patency was established in one or both tubes and marriage effected with fertility status in the husband satisfactory, no therapy would be instituted except mild

analgesics followed by a thorough discussion of the nature of the disease and its benign behavior pattern. Increasing reports of malignancy arising out of endometrial implants does not deter me from reassuring these people.

There would be no indication here for the use of estrogens or androgens resulting in anovulatory periods unless pain or bowel involvement with obstructive symptoms were present. The short period of fertility left in 42-year-old woman, handicapped by the high percentage of infertility (35 per cent in victims of endometriosis) makes each month with ovulation of the utmost importance.

The medical management of endometriosis is rapidly becoming one of the more definitely delineated therapeutic regimens in gynecology.

The observations resulting in Meigs' statements encouraging early marriage with pregnancy as prophylaxis and several clinical reports establishing pregnancy as curing or arresting the disease gives gestation the prime consideration in its medical management. Karnaky with later confirmation by Willard Cooke and others demonstrated the regression and possible obliteration of endometriotic lesions by the suppression of the adeno-hypophysis with synthetic estrogen-like substances. The danger of withdrawal bleeding may be reduced by gradually withdrawing the drug after 3 or more months. The animal experiments of Scott did not confirm Karnaky's observations, but clinical studies supported it.

The use of androgens has proved most valuable in management of cases with minimal to moderate involvement through periods of discomfort produced by increased activity of the ectopic endometrial glands. Ten milligrams of methyltestosterone daily by mouth through two menstrual cycles in many instances will give symptomatic relief although the rationale may be argued. Higher doses will inhibit ovulation but masculinization symptoms may result and should be avoided.

The use of the newer progestins and their results are most easily rationalized. Kistner

states that a decidual reaction can be brought about in both the endometrium and the ectopic implants by the prolonged administration of estrogens and progestins. It is suggested that the decidual cells undergo a gradual process of necrosis which is subsequently followed by liquefaction and absorption. Side effects of nausea, fluid retention, and other unpleasant effects may make intolerable the continuation of recommended courses of therapy. It is well here to say that the use of prolonged acting progestational elements must be reviewed continuously and critically by the clinician and that the decision to employ the same be predicated on evaluation of indications just as critically as for surgical procedures.

In closing, it must be said that only a small percentage of patients with endometriosis have symptoms that require more than an intelligent discussion of the problem and mild analgesic. Many of the ovarian endometriomas regress spontaneously under observation without therapy. The few patients who cannot benefit by the now recognized effects of pregnancy and because of infertility or pain have to be subjected to operation may be managed conservatively with excellent results.

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This case does not offer a diagnostic challenge, for the diagnosis is given; however, there are certain aspects in the presentation which are worthy of comment. Can this individual be considered to have an infertility problem on the basis of the information which is given? We do not know the duration of the previous marriage, the desire for pregnancy during this previous marriage, whether the previous abortion was spontaneous or induced, or the interval since her divorce. These may seem to be unimportant, yet all too often results of surgical

or hormonal therapy are based upon extrapolations from such incomplete histories.

Abnormal uterine bleeding has frequently been listed as a common symptom of endometriosis. In our experience the ovaries continue to function remarkably well despite extensive involvement, and, when the other possible and probable causes of abnormal uterine bleeding are excluded as etiological factors, abnormal uterine bleeding is a true symptom of external endometriosis in no more than 12 to 20 per cent of the cases. Also, acquired or increasing dysmenorrhea as a symptom of external endometriosis is present in only about 25 per cent of patients; this patient had no dysmenorrhea, for her pain was obviously secondary to peritoneal irritation from leakage of old blood. Did the medical survey include an adequate pelvic examination? I assume that it did, for she had two previous curettages and an adequate pelvic examination under anesthesia should be mandatory. This patient had uterine fibromyomas, but it is not unusual for indurated, thick-walled, adherent endometrial cysts to adhere to the uterus and simulate fibromyomas to even the most experienced examiner. Shoulder pain is usually associated with extensive peritoneal irritation from a large amount of noxious material. It is most unusual secondary to leakage from or even overt rupture of an endometrial cyst.

In gynecological examinations entirely too much importance is placed upon the production of pain by motion of the cervix. Pelvic inflammatory disease, leaking endometrial cysts, tubal pregnancies, ruptured corpus luteum hematomas, diverticulitis, acute cystitis, spastic bowel, and most any pelvic disease or complaint (including those of the psychoneurotic individual with pelvic fixation of her symptoms) can be accompanied by this nonspecific finding on examination.

The "medical survey" continues to interest me. No mention is made of pelvic examination as a part of the medical survey; there is no mention either of cytological examination. This recalls the medical investigation

of a famous actress, whose first pelvic examination was prompted by the finding of pulmonary metastases from a cervical cancer at the time of her fifth admission.

The preoperative diagnosis was correct and the statement is made that the patient "volunteered" the information that she was planning marriage and that she wished to retain her childbearing function. Gynecological surgery is not simply a personal assessment *by the surgeon* of the pathological process and then his *personal* opinion of what is best for the patient. Lay literature has disseminated to the point that a reasonable discussion of the problem with the patient is not only rewarding but is a part of proper caring for the patient; the patient must express her desires and the surgeon must present possibilities and probabilities, always retaining the option of using his best judgment at the time. In this particular case the preoperative diagnosis was correctly made and the future plans and the desires of the patient were ascertained. The patient must be told that conception becomes increasingly difficult after age 40, spontaneous abortions and premature deliveries are more common, certain anomalies (such as Mongolism) are seen more often, and fibromyomas and endometriosis can necessitate subsequent operations if reproductive function is preserved. If in the face of adequate discussion and presentation of this calculated risk the patient desires a conservative operation, then every effort should be made to abide by this desire, *provided* it is a reasonable approach at the time of definitive operation. As an example, I recall the case of a 43-year-old woman during her second marriage who had uterine fibromyomas, symptoms of submucous extension, and palpable endometriosis; she refused operation until she found an individual sufficiently interested in her problem to agree to a conservative procedure, *if feasible*. Twenty-six fibromyomas were removed (including two submucous ones), areas of endometriosis excised or fulgurated, the uterus and ovaries suspended, and a presacral neurectomy performed. She was delivered at term by

cesarean section 18 months later and the patient, her husband, and her surgeon have shared the reward in this satisfactory outcome.

In this particular case a conservative operation has been requested and I assume that the surgeon has agreed to preserve reproductive function if possible and if it does not seriously conflict with his best surgical judgment at the time. The right endometrial cyst had ruptured; as a general rule the endometrial tissue in the wall of such a cyst is unhealthy from compression necrosis and incapable of peritoneal implantation. This reasoning has clinical support since most endometrial cysts rupture when an attempt is made to free them surgically, and peritoneal or incisional implants are rarely seen secondary to such rupture. Some of the "hemorrhagic spots" in the pelvic peritoneum may be areas of pre-existing endometriosis, but most of them are probably foci of peritoneal reaction to old blood. It is most unfortunate that the patent tube and the normal ovary were not on the same side. A tuboplasty on a hydrosalpinx is rarely successful and I would consider it only if no reasonable remnant of normal ovarian tissue can be found in the right ovary. The first choice would be resection of the ovarian cyst from the right ovary and suspension of the ovarian remnant to the peritoneum just above the pelvic brim; the left tube and ovary should be removed to ensure that the right ovarian remnant would subsequently receive the full impact of pituitary stimulation. If no reasonable normal ovarian tissue can be found on the right, then this ovary should be removed, the left ovary freed and suspended and a tuboplasty over a polyethylene prosthesis performed on the left tube. The subserous myomas can be shelled out and the uterine peritoneal incision covered with pieces of omental tissue to reduce intestinal agglutination. All endometrial implants should be excised or fulgurated.

In this particular patient I doubt that a presacral neurectomy need be done. Formerly, at the time of conservative operation in a younger patient a presacral neurectomy

was done if dysmenorrhea were a presenting symptom; more recently, a presacral neurectomy has been performed as a regular part of the conservative procedure, even in the absence of pain. A sufficient number of conservatively treated patients without presacral neurectomy have subsequently developed dysmenorrhea or pelvic pain from recurrent or residual endometriosis that I have condemned myself for neglecting this surgical adjunct.

Past the age of 40, it is generally sound surgical judgment when endometriosis is encountered to remove all ovarian tissue and the uterus. In this particular instance the operation was tailored to fit the patient's desires. Granted, her chances of a viable term pregnancy are slim, but it is also true that the chances of subsequent surgical procedures for recurrence of the endometriosis or for symptomatic myomas are also slim. She has been left with menstrual function and with at least the potential of conception.

The request was made to discuss the treatment of external endometriosis in general. It is my personal opinion that endometriosis is present in all women 40 years of age who have patent tubes; serial section of all of the pelvic tissues would be necessary to establish this hypothesis. In my recent personal experience it has been possible to demonstrate histological endometriosis in approximately 75 per cent of all pelvic laparotomies, no matter what the primary indication, provided all suspicious pigmented spots or areas of scarring are separately excised and studied. Clinically palpable nodularity and thickening in the pelvis suggestive of endometriosis is as common as small myomas at the time of routine pelvic examination. The vast majority of these patients are asymptomatic or the symptoms are amenable to relief by mild analgesics; these patients need only reassurance and periodic examination and evaluation.

Pregnancy is a well-recognized treatment measure for this disease. Admittedly, fertility is impaired in the presence of this disease, but if it is possible for the patient to con-

ceive there is reasonable clinical assurance of relief of symptoms during the pregnancy and there is usually a 2 to 5 year interval following delivery before symptomatic exacerbations are seen. The young lady with palpable evidence of endometriosis during premarital examination should be urged to re-evaluate her family planning and attempt pregnancy as soon as reasonably desirable after marriage.

Operation is the treatment of choice for external endometriosis when both the symptoms and palpable findings are of sufficient magnitude. By the surgical approach it is possible to tailor the procedure in most instances to fit the desires of the patient; all evident endometriosis can be excised or destroyed and fibrosed by fulguration; anatomic realignment performed to prevent agglutination of tissues and spread by continuity; subsequent discomfort reduced or prevented by a presacral neurectomy; if the preservation of reproductive function is not possible or desired, a hysterectomy can be done and some ovarian tissue preserved; the diagnosis can be established; and a potentially malignant or malignant ovarian neoplasm can be ruled in or out and properly treated. It is not possible to palpate mitoses in an ovarian cyst which persists or enlarges under observation. I have found it necessary to resect large bowel twice and small bowel twice as a part of the conservative treatment of endometriosis. If extensive bowel involvement is encountered and the preservation of reproductive function not essential, it would be inadvisable to leave any ovarian tissue. If the lesion in the bowel has already produced obstructive symptoms, bowel resection should be done, even though all ovarian tissue has been removed. The rewards certainly justify the conservative surgical procedure. At the University Hospitals of Cleveland over a recent 15 year period, 103 conservative surgical procedures were done in the treatment of this disease; 66 patients (or 64 per cent) conceived subsequently and 54 (or 52.4 per cent) were delivered of term infants. During the period of follow-up, which extended from 1 to 16 years, only 10 (or less than 10

per cent) of these patients had to have subsequent operations for endometriosis.

The retention of ovarian tissue if hysterectomy is done for endometriosis is debatable. It serves some psychic value and it is my opinion that a portion of one ovary is worth a bushel of prescription pad hormones for the woman in her late 20's or 30's. Excision and fulguration of all endometriosis and hysterectomy practically always give symptomatic relief; Javert feels that the normally located endometrium can extend through myometrial lymphatics to external areas, but a more logical explanation of the relief by hysterectomy is the absence of an organ with its periodic call for blood, the absence of dysmenorrhea, and the absence of a large and interposing organ for agglutination and pressure. If ovarian tissue remains and symptoms return, the diagnosis is known and radiation castration is easily done. At times fragments of ovarian tissue are left behind inadvertently, symptoms may continue and again radiation castration is the treatment of choice. I know of one instance in which three surgical procedures did not succeed in removing all functioning ovarian tissue.

Where does hormone treatment fit into the picture? In my experience it is only the rare patient with external endometriosis who has sufficient symptoms to warrant extensive hormonal therapy in preference to operation. Possibly there is a place for them in the younger, unmarried woman who has only minimal palpable disease or the woman who has a recurrence following conservative operation. At the present writing there is no evidence that any of the various types of hormone treatment are curative, either from the clinical or the animal experiments. Estrogens will inhibit ovulation and in increasing doses can produce amenorrhea; if uterine bleeding ensues during the treatment, it can be postulated that some of the areas of endometriosis will bleed, and despite the best planned schedules severe uterine hemorrhage as a problem may be substituted for the pain in association with endometriosis. Androgens in large doses are virilizing. Most women

have more hair than they want anyway, and they also resent the other masculinizing symptoms. Androgens in small doses do not inhibit ovulation and at times can reduce the symptoms; if they are used it should be understood that it is a temporizing measure, the dosage must not exceed 150 to 200 mg. a month, and they should not be continued for more than 3 or 4 months. The reported increase in fertility under and following androgen therapy needs confirmation.

Recently the progesterone-like substances have been advocated. Any day now I expect the ads to show a "before" woman writhing in pain and the "after" woman with the appropriate facial satisfaction enjoying an evening of dancing at The Savoy. The producers of these various substances have certainly used the diaper, safety pin, and baby carriage to the point of nausea. Theoretically a "pseudo-pregnancy" is produced, ovulation is inhibited, and possibly there will be a subsequent atrophy or fibrosis of the stroma in the areas of external endometriosis. By this reasoning the advocates claim that the relief of pain is similar to the relief during pregnancy and they hope for the period of relief following treatment. Clinical studies are in progress and it is too early to evaluate the long-term results. On an increasing dose schedule the patients are relieved of their symptoms, but not enough of them have been followed for a sufficient period after treatment.

I suspect that the postpartum relief for a period of time is more likely due to the dilatation of the cervix by delivery and the thereby lessened possibility of retrograde tubal menstruation than it is from atrophy of the necrotic decidual tissue. The cost of these progesterone-like substances is no insignificant item.

There is a place for the use of hormones in the treatment of a few selected patients with endometriosis, but it must be realized that this treatment is a temporizing one and not curative. Recently I have been using the progestroids on a constant, not increasing dose schedule for about 8 weeks before contemplated operation; the operation is easier,

the cleavage planes are better established, and the areas of external endometriosis are more evident because they have hemorrhage in them.

Editor's comment

This case demonstrates well that individualization in treatment of patients with endometriosis is necessary. It also demonstrates the individual differences in gynecological management in dealing with the same clinical problem. My experience with patients in whom endometrial cysts have spontaneously ruptured is quite different from that expressed in the consultations. The recurrence of the endometriosis and the resumption of severe symptoms subsequent to conservative surgical procedures are more likely to occur after spontaneous rupture than in cases without rupture, so much so in fact that more radical surgical procedures are usually performed under these circumstances. The three episodes in a period of 2 years of intraperitoneal bleeding from repeated rupture of ovarian endometriosis with severe symptoms and incapacitation in a patient 42 years of age are indication for operation. The extent of the procedure should be consistent with the wishes of the patient but also with good surgical judgment. As intimated in the consultations, one of the best ways to assure conservation of childbearing functions is to avoid a surgical procedure until the patient has had her desired number of children. All too often a procedure started with the intent of being conservative ends either in being more radical than intended or in being conservative but inadequate from a surgical standpoint. It is with these thoughts in mind that I prefer to delay surgical procedures until forced into them by severity of the disease, the extent of the lesion, or the development of an ovarian tumor. It is always possible that the latter is a neoplasm rather than an endometriotic cyst even though by bimanual examination the presence of endometriosis in the cul-de-sac is obvious.

One of the Consultants mentioned a point that I wish to stress, namely, that the sur-

geon and for that matter all physicians should discuss freely with the patient the problem of her disability and the procedures to be performed. It is essential that the patient understand the entire situation and

that the surgeon or physician can prove, in a court of law if necessary, that the problems and contemplated procedures were fully explained to the understanding of the patient.

Reviews | Abstracts

Edited by

LOUIS M. HELLMAN, M.D.

Book reviews

First Canadian Symposium on Non-gonococcal Urethritis and Human Trichomoniasis.

By Zoltan Gallai and Lucien Sylvestre. Parts 3 and 4, 170 pages, illustrated. White Plains, N. Y., 1960, Albert J. Phiebig. \$5.80.

The problem of the treatment of *Trichomonas* vaginal infections has been a field of constant investigation ever since pathogenic properties were first attributed to this flagellate by Hoehne, 1916. The salient features of these investigations are discussed by R. Chappaz in the main lecture of this symposium. Many of the following articles cover similar material. There seems to be general agreement that *Trichomonas* infection is a venereal disease and that both sexual partners must be treated in order to obtain satisfactory results. Many forms of therapy with different agents are discussed, but with few exceptions the long-term cure rate has been uniformly disappointing. One of these exceptions is the use of vaginal and urethral Stovarsol suppositories

twice daily for a period of 2 weeks. However, the author, J. Bedoya, points out that this form of therapy is cumbersome, and a more easily administered drug is much needed.

The experimental work of Feo shows that when systemic therapy is utilized, the drug concentration of the vaginal secretions does not reach therapeutic levels. However, the urinary tract which is a significant site in chronic forms of *Trichomonas* infestations, is successfully cleared. It becomes evident that when the proper chemotherapeutic agent is found a combination of systemic and local therapy is indicated.

The psychosomatic aspect of symptomatic *Trichomonas* vaginitis is amply discussed. In one series careful history revealed some degree of emotional instability in approximately 80 per cent of the patients with the chief complaint of vaginitis.

The excellent electron photomicrographs by S. Inoki and associates are helpful in understanding the anatomy of this elusive pathogen.

Books received for review

Adrenergic Mechanisms. Edited by G. E. W. Wolstenholme and M. O'Connor. 632 pages, 163 illustrations. Boston, Mass., 1960, Little, Brown & Company. \$12.50.

Annales Chirurgiae et Gynaecologiae Fenniae. Edited by K. E. Kallio and P. Vara. 300 pages. Helsinki, 1958, Mercatorin Kirjapaino.

Das Carcinoma Colli Uteri Seine Prognose und Behandlung. By V. W. Janisch-Raskovic. 649 pages, 76 illustrations. Leipzig, Germany, 1960, Veb Georg Thieme. DM 75.

Childbirth With Hypnosis. By W. S. Kroger. 216 pages. Garden City, N. Y., 1961, Doubleday & Co. \$3.95.

Clinical Disturbances of Renal Function. By A. G. White. 468 pages, 90 figures. Philadelphia, 1961, W. B. Saunders Company. \$10.50.

Curso Elemental de Ginecologia Patologia Obstetrica. By J. B. Llusia. Fifth edition. 705 pages, 449 figures. Barcelona, 1961, Editorial Cientifico-Medica.

- Dunham's Premature Infants.** By W. A. Silverman. Third edition. 578 pages. New York, 1961, Paul B. Hoeber, Inc. \$15.
- From Girlhood to Womanhood.** By A. Sharman. 72 pages, 4 figures. Baltimore, 1960, Williams & Wilkins Company. \$1.75.
- Gynäkologische Urologie.** By W. Langreder and H. Schwalm. 306 pages, 135 illustrations, 9 tables. Stuttgart, Germany, 1961, Georg Thieme Verlag. \$14.05.
- Information, Please! For Women Only.** By A. Dreyfus. 556 pages. New York, 1961, Vantage Press, Inc. \$7.50.
- Die Intersexualität.** By C. Overzier. 560 pages, 193 illustrations, 38 tables. Stuttgart, Germany, 1961, Georg Thieme Verlag. \$28.35.
- Istopatologia Ginecologica e Gravidico-Coriale.** By G. B. Candiani and G. Remotti. 274 pages. Milan, Italy; 1960, Societa Farmaceutici Italia.
- Management of Obstetric Difficulties.** By J. R. Willson. Sixth edition. 687 pages, 323 figures. St. Louis, 1961, The C. V. Mosby Company. \$16.50.

- Medical Almanac 1961-1962.** By P. S. Nagan. 502 pages. Philadelphia, 1961, W. B. Saunders Company. \$5.
- Metabolic Effects of Adrenal Hormones (Ciba Foundation Study Group No. 6).** Edited by G. E. W. Wolstenholme and M. O'Connor. 109 pages. Boston, 1960, Little, Brown & Company.
- Moral Principles of Fertility Control.** By D. O'Callaghan. 39 pages. Dublin, 1961, Clonmore & Reynolds, Ltd. 2/6d.
- Die praoperative Rontgenbestrahlung des Mammakarzinoms.** By E. Muntean. 108 pages, 26 tables, 9 illustrations. Stuttgart, Germany, 1961, Georg Thieme Verlag. \$4.40.
- Report of the Second Institute on Clinical Teaching.** Edited by H. H. Gee and C. G. Child. 199 pages. Evanston, Ill., 1961, Association of American Medical Colleges.
- A Textbook for Midwives.** By M. F. Myles. Fourth edition. 776 pages, 389 figures. Baltimore, 1961, Williams & Wilkins Company. \$8.50.

Selected abstracts

Acta obstetrica et gynecologica scandinavica

Vol. 39, 1960.

- *Sandberg, F., Ingelman-Sundberg, A., Lindgren, L., and Ryden, G.: In Vitro Studies of the Motility of the Human Fallopian Tube, p. 506.
- *Brody, S., and Westman, A.: Ovarian Hormones and Uterine Growth, p. 557.
- *Brody, S., and Westman, A.: Studies on Hormonally Induced Uterine Growth, p. 566.
- *Hirschfeld, J., and Soderberg, U.: The Unsaturated Capacity of the Thyroxine-Binding Proteins in Pregnant Women and Newborn Infants, p. 645.
- Sandberg et al.: In Vitro Studies of Motility of Human Fallopian Tube, p. 506.**

The spontaneous motility of Fallopian tubes from 75 patients of reproductive and postmenopausal age have been studied by the Magnus-Kehrler

technique. After a period of adaption of about one hour, the spontaneous motility of the longitudinal muscles in the four anatomically defined parts of the tube was recorded isotonicly with optimal load for half an hour. The effect of acetylcholine, epinephrine, norepinephrine, and oxytocin has been investigated, each drug added to the bath solution for about 20 minutes.

The similarities of the response of the Fallopian tube to acetylcholine, epinephrine and norepinephrine are increased tone and amplitude maximum for all three drugs. There were no differences in response to the drugs tested between the isthmus part and the other parts of the tube. For these drugs the incidence of response in the menopausal group is almost the same as in the reproductive age groups. The sensitivity to norepinephrine is increased in the secretory phase, however, and the sensitivity to acetylcholine is increased in the proliferative phase of the menstrual cycle.

In contrast to these findings, oxytocin has a spasmolytic action on the Fallopian tube, but no difference in response was noted in the

*These articles have been abstracted.

various segments. There was a rather low incidence of response with decreased tone and amplitude maximum, irrespective of the sexual phase. Concerning oxytocin, there is, however, a qualitative difference in response between the Fallopian tube and the uterine corpus. On the tube, oxytocin has a spasmolytic action, but on the corpus the action is mainly stimulatory.

Robert E. L. Nesbitt, Jr.

Brody and Westman: Ovarian Hormones and Uterine Growth, p. 577.

The present investigation has shown an appreciable increase in the size and weight of the rabbit uterus induced by estradiol, either alone or following previous progesterone treatment. The biochemical elucidation of the problem of type of growth, whether hypertrophic or hyperplastic, has been made possible by the discovery of the average constancy of the DNA-phosphorus (DNAP) content per somatic nucleus. This average constancy of DNAP per nucleus permits calculation of the number of nuclei in a tissue under study. The effects of estradiol-17 β have been investigated by measuring wet and dry weight, desoxypentose nucleic acid concentration, and the extent of net synthesis of this latter cellular component. In the present paper the tissue unit has been used as preferable to the per-cell unit of DNAP.

The results indicate that estradiol under the experimental conditions obtaining induces uterine growth exclusively by hypertrophy (increase in cell mass). Estradiol after previous progesterone administration causes growth of the rabbit uterus by hypertrophy as well as by hyperplasia (increase in cell number). Under the conditions obtaining in this experiment, the activation of metabolic processes associated with cellular reduplication seems to require the interaction of at least two types of hormones. The study further demonstrates that progesterone effects are elicited even in castrated animals that have not been pretreated with estrogenic hormone. This might be interpreted as indicating a stimulation of certain cellular systems concerned with hyperplastic growth. It may be that following treatment of castrated rabbits with progesterone, estradiol triggers these metabolic functions of the cell, thereby inducing the hyperplastic type of growth. It may be that the species specificity explains the apparent contradiction between these results and the reported findings of estrogen-induced endometrial hyperplasia in primates.

Moreover, the extent of DNA net synthesis associated with this process may be of an order of magnitude that escapes detection under the present conditions.

Robert E. L. Nesbitt, Jr.

Brody and Westman: Studies on Hormonally Induced Uterine Growth, p. 566.

The influence of estradiol-17 β , either alone or after previous progesterone administration, on the desoxyribonuclease activity of the castrated rabbit uterus has been studied. The present investigation clearly shows a considerable increase in the cellular DNase levels. Pretreatment with progesterone does not seem to influence the magnitude of the DNase increase to any appreciable extent. The results indicate that the rise in DNase activity is associated with the hypertrophic growth phase of the cell. The results clearly show that in hormonally induced growth increase in dry mass, DNase activity, and total amount of PNA preceded any measurable net synthesis of DNA. The highest cellular levels of desoxyribonuclease activity were associated with the period of most intense desoxypentose nucleic acid net synthesis. The close time-relationship between DNase activity and new formation of DNA definitely points to a functional association between this enzyme and the metabolism of DNA. In the estradiol group there was a close time-relationship between the increase in desoxyribonuclease activity and dry mass per tissue unit. In the progesterone-estradiol group the change in dry mass lagged somewhat behind the increase in enzymatic activity. The results of the present investigation are in line with the interpretation that DNase in normal growth may be involved in cellular mechanisms controlling the extent and rate of DNA net synthesis and cellular multiplication.

Robert E. L. Nesbitt, Jr.

Hirschfeld and Soderberg: Unsaturated Capacity of the Thyroxine-Binding Proteins in Pregnant Women and Newborn Infants, p. 645.

It is generally believed that thyroxine is attached to at least three plasma proteins, the so-called thyroxine-binding globulin (TBG or TBP), albumin, and a protein which migrates anodal to albumin in most electrophoretic systems, and is therefore called prealbumin. The unsaturated capacity of the thyroxine-binding proteins in pregnant women and newborn infants

has been studied with a new technique and compared with serum protein-bound iodine and cholesterol. The method employs a stepwise titration of the protein-binding of thyroxine labeled with I^{131} and added to serum, the components of which are separated by agar-gel electrophoresis. Radioautographs were made by covering the agar-gel covered plates with no-screen x-ray film. After exposure, the plates were stained with Amidoblack 10 B. The labeling of the serum proteins is proportional to the absolute amount of thyroxine bound by the proteins.

Serum of 57 pregnant women and of their 62 infants was tested for thyroxine-binding at the moment of birth. In uncomplicated pregnancies there was generally a marked increase in maternal thyroxine-binding globulin (TBG) and PBI. Serum from newborn infants showed essentially the same values as that of nonpregnant adults or, occasionally, a slight rise in TBG. Absence of rise in TBG and PBI was found to be an early sign of threatened abortion, but abortion can occur in patients with increased TBG; and, furthermore, a low TBG and PBI were recorded from one apparently normal healthy woman who was delivered of a normal infant. These observations demonstrate that an increase in PBI and TBG is not a prerequisite for uncomplicated pregnancy.

Since it is apparent that thyroid activity is regulated through a feedback mechanism in the fetus (TSH apparently does not cross the placenta), the low capacity of the thyroxine-binding proteins of the fetus might play a role in the early development of the thyroid by preventing too much maternal thyroxine from entering the fetal circulation early in pregnancy. Since thyroxine inhibits thyroid activity directly, TSH is not necessary. The thyroxine inhibition might have a function in fetal life by initiating a direct feedback circuit.

Robert E. L. Nesbitt, Jr.

Suppl. 3, 1960.

*Vehaskari, A.: The Operation of Choice for Ectopic Pregnancy With Reference to Subsequent Fertility, pp. 1-41.

Vehaskari: Operation of Choice for Ectopic Pregnancy With Reference to Subsequent Fertility, pp. 1-41.

This investigation was based on a series of 366 cases of ectopic pregnancy (250 of tubal abortion, 114 of ruptured tubal pregnancy, one of primary abdominal pregnancy, and one of

ovarian pregnancy). In 6 per cent (22 cases) the operation resulted in definite sterility. In 246 cases the pregnant tube was removed by the ordinary salpingectomy or salpingo-oophorectomy ("normal" operation). In 67 cases the removal of the tube was accompanied by contralateral salpingolysis or salpingostomy ("restorative" operation). In 31 cases the pregnant tube was spared ("conservative" operation), and in some instances this procedure was accompanied by repair of the contralateral tube.

Excluding the "sterilized" group of patients, 89.5 per cent of the group of patients who were subjected to a "restorative-conservative" procedure was followed up. The average period of postoperative hospital treatment was 9.8 days, and the incidence of complications was 11.8 per cent in the whole series. It was no higher in the group of "restorative-conservative" operations than in the group of "normal" operations.

Of all patients who were followed up, 48.2 per cent (148 patients) became pregnant and 33.5 per cent (103 patients) bore children. In the group of "restorative-conservative" operations, the corresponding figures were 49 per cent and 30 per cent; or roughly similar to those in the group of "normal" operations, 48.0 and 35.2 per cent, respectively. Ectopic pregnancy recurred in 10.4 per cent of the cases (32 patients) in the whole series. In the group of "restorative-conservative" operations, the corresponding incidence was 16 per cent, or approximately twice as high as in the group of "normal" operations, in which it was 8.2 per cent. The former incidence of postoperative ectopic pregnancy is from five to eight times as high in the group of "restorative-conservative" operations as the incidence reported in publications dealing with the surgical treatment of the tubal sterility of nonpregnant women.

Robert E. L. Nesbitt, Jr.

Canadian Medical Association Journal

Vol. 83, No. 21, Nov. 19, 1960.

*DeVries, J. A., and Salisnjak, M. M.: Disinfection of Nurseries Contaminated With Staphylococci, p. 1082.

DeVries and Salisnjak: Disinfection of Nurseries Contaminated With Staphylococci, p. 1082.

A method of disinfecting nurseries is outlined. A chlorinated phenol is applied in a miscible soap base as a washing compound and in an alcohol-propylene glycol mixture as an aerosol.

The empty nursery is sprayed with the aerosol mixture and then washed with the soap mixture, and the remaining disinfectant in the air is removed by vacuum filtration.

Cultures from the nurseries were taken before and after disinfection in 19 separate tests. In each instance the nursery was thoroughly contaminated before cleaning but no staphylococci could be found after disinfection.

The germicidal properties of a mixture of a disinfectant and a detergent were greater than when a disinfectant or a detergent was used alone.

Colonization of newborn infants by *Staph. pyogenes* was investigated bacteriologically by taking daily cultures from their noses and feces. All the babies became carriers of *Staph. pyogenes* before their discharge from the hospital, although in 4 colonization was intermittent. No attempt was made to trace the mode of spread of the organisms.

John J. Dettling

Vol. 83, No. 23, Dec. 3, 1960.

*Quinn, L. J., McKeown, R. A., Moore, T., and Dorr, H. P.: Abdominal Decompression During the First Stage of Labour: A Preliminary Report, p. 1192.

Quinn et al.: Abdominal Decompression During the First Stage of Labour, p. 1192.

This is a preliminary report of abdominal decompression as a method of reducing the pain of parturition and of accelerating the first stage of labor. The history and theory of action of abdominal decompression have been discussed. A new method for decompression, using a thermoplastic chamber that fits over the breasts and abdomen, has been described.

Only 7 of the 46 patients took more than 5 hours to reach full dilatation. The first stage of labor was markedly accelerated in primigravidas, and to a lesser extent in multigravidas. The technique gives very definite relief of pain. Only 21 of 46 patients (45.6 per cent) received any sedation, and many of these could have managed without it.

Abdominal decompression may be capable in some instances of converting prodromal labor into an unequivocal type of labor. The average time of decompression (from 4 cm. or less to full dilatation) was 2 hours and 56 minutes for primigravidas and 1 hour and 57 minutes for multigravidas.

The authors feel that further trial is war-

ranted, as this method of decompression may be a very important addition to the conduct of the first stage of labor.

John J. Dettling

General Practitioner

Vol. 22, No. 6, December, 1960.

*Benson, R. C.: Treatment of Thyrotoxicosis During Pregnancy, p. 116.

Benson: Treatment of Thyrotoxicosis During Pregnancy, p. 116.

The incidence of true hyperthyroidism in pregnancy is 2 to 3 per 1,000 pregnancies. This frequency is not altered by race, age, or parity.

The adenomatous hyperplasia of the thyroid gland noted in normal pregnancy is accompanied by increased uptake and retention of iodine. In consequence, levels of circulating globulin-bound thyroid hormone are increased. These changes are not accompanied by clinical hyperthyroidism. The reason for the lack of clinical disease is a rise in the thyroxine-binding capacity of serum alpha globulin to about two and one-half times that of the normal nonpregnant adult. This rise in binding capacity begins as early as the third gestational week, and persists until the fourth to sixth postpartum week. Thus, in spite of the elevated serum iodine level, the level of free thyroxine is lower in the pregnant than in the nonpregnant woman.

The clinical diagnosis of hyperthyroidism is more difficult in the pregnant than in the nonpregnant state. One is also handicapped in the use of the laboratory during pregnancy. Radioiodine is not without hazard due to fetal irradiation, although the use of the short half-lived isotopes I^{132} and I^{133} may obviate this danger. Tests involving thyroid-stimulating hormone are of no value during pregnancy, as this hormone increases promptly after conception, and no baseline levels are known for normal pregnancy. In general, clinical impression and the serum butanol-extractable iodine or protein-bound iodine must be relied upon for diagnosis.

The treatment of hyperthyroidism in pregnancy is limited. Radioactive iodine therapy is very dangerous to the fetal thyroid. Use of thiourea derivatives may be attended by fetal goiter or hyperthyroidism. Iodine, in the form of Lugol's solution, potassium iodide, or syrup of hydriodic acid "may well be the drug of choice." Generally, the incidence of recurrence of toxic goiter with medical therapy is twice as great as that following surgical procedures.

Subtotal thyroidectomy remains the major form of therapy in pregnant patients with moderate or severe Graves disease. The operation is preceded by 2 weeks of iodine therapy to reduce vascularity and friability of the gland.

Any mode of therapy that leads to maternal hypothyroidism may increase the incidence of abortion or of fetal anomalies. Tri-iodothyronine in small doses rapidly corrects the manifestations of hypothyroidism, but, since this drug acts at the cellular level, the BEI or PBI will not reflect this improvement, and one must depend upon clinical evaluation. The improvement due to thyroxine administration, on the other hand, is reflected in these tests. *Carl J. Pauerstein*

Indiana Law Journal

Vol. 35, No. 2, Winter, 1960.

Weinberger, A. D.: A Partial Solution to Legitimacy Problems Arising From the Use of Artificial Insemination, p. 143.

Journal of Clinical Endocrinology and Metabolism

Vol. 20, No. 8, August, 1960.

*Albert, A., and Derner, I.: Studies on the Biologic Characterization of Human Gonadotropins. V. Comparison With Sheep Luteinizing Hormone, p. 1059.

*Simkin, B., and Goodart, D.: Prolactin Activity in Human Blood, p. 1095.

Albert and Derner: Biologic Characterization of Human Gonadotropins, p. 1059.

Seven assays were carried out for sheep luteinizing hormone (LH) by the method of simultaneous response of the ovary and uterus in the intact mature rat. The parameters of these assays were then compared with similar constants derived from assays for human pituitary gonadotropin (HPG) of urine. The shapes of the dose-response curves for LH were greatly different from those for HPG. The response to LH is biphasic, consisting of a small increment in growth of both ovary and uterus, followed by a plateau, after which another increment in ovarian and uterine growth occurs. The response to HPG of both ovary and uterus is a linear function of the log of the dose. LH also is less effective than HPG in inducing estrogenic secretion in this assay system. It was concluded that HPG, although it possesses the biologic properties of LH in addition to its follicle-stimulating properties, is totally dissimilar to purified LH in this assay system. *J. Edward Hall*

Simkin and Goodart: Prolactin Activity in Human Blood, p. 1095.

Prolactin activity of human whole blood was concentrated by means of acid acetone extracts by means of the Sulman method for the extraction of chromotrophotropic activity. These extracts were assayed by a single injection local pigeon crop-weight technique. No prolactin activity was found in extracts obtained from the blood of children, of normal young men, and of normal young women in the first half of the menstrual cycle. On the other hand, extracts obtained from the blood of young women in the second half of the menstrual cycle induced crop-weight responses of the same order of magnitude as induced by 0.05 I.U. of authentic prolactin, and activity greater than this was found in extracts obtained from the blood of lactating postpartum women. These observations constitute physiologic evidence that prolactin activity was measured, since prolactin activity was found only in those circumstances that would be expected on the basis of the known physiologic activity of the hormone. Further physiologic evidence was provided by the disappearance of prolactin activity in the blood of adult female rats and an oophorectomized woman 1 to 2 weeks following hypophysectomy. Technically, the ability to confirm positive local prolactin assay results by positive systemic assay results with the use of pooled extracts further support the validity of these observations. The complete recovery of small amounts of prolactin by the Sulman extraction technique is another piece of technical evidence supporting the concept that prolactin activity was demonstrated in human blood.

J. Edward Hall

No. 9, September, 1960.

*Albert, A., and Derner, I.: Studies on Biologic Characterization of Human Gonadotropins. VI. Nature and Number of Gonadotropins in Human Pregnancy Urine, p. 1225.

Albert and Derner: Biologic Characterization of Human Gonadotropins, p. 1225.

Assays of human chorionic gonadotropins (HCG, urine) were conducted by measuring the simultaneous response of the ovaries and uteri of immature intact female rats over a dose range of 0.1 to 30,000 I.U. per animal. Uterine stimulation began at 0.25 I.U., was maximal at 1.0 I.U. and remained maximal between 1.0 and 30,000

I.U. The shape of the curve denoting uterine response as reported previously was that of an autocatalytic curve. Ovarian growth was induced at about 5 I.U. and proceeded at a low slope until about 35 I.U. Ovarian weight increased, then ceased at a plateau of about 40 mg., between doses of 35 and 840 I.U. After this, ovarian growth resumed at an accelerated pace. The shape of the ovarian response curve is thus diphasic. When the complete dose-response data were plotted in absolute coordinates, it was possible to compare HCG with human pituitary gonadotropin (HPG). The parameters of the dose-response of HCG are not the same as those of HPG. These results are favorable to the concept that HCG has intrinsic follicle-stimulating properties and are unfavorable to the concept that the human pituitary gland secretes gonadotropin during pregnancy.

J. Edward Hall

No. 11, November, 1960.

*Apostolakis, M., and Loraine, J. A.: Renal Clearance of Pituitary Gonadotropins in Postmenopausal Women, p. 1437.

*Doe, R. P., Zinneman, H. H., Flink, E. B., and Ulstrom, R. A.: Significance of Concentration of Non-protein-bound Plasma Cortisol in Normal Subjects, Cushing's Syndrome, Pregnancy, and During Estrogen Therapy, p. 1484.

*Krieger, D. T., Gabrilove, J. L., and Soffer, L. J.: Adrenal Function in a Pregnant Bilaterally Adrenalectomized Woman, p. 1493.

Apostolakis and Loraine: Renal Clearance of Pituitary Gonadotropins in Postmenopausal Women, p. 1437.

The renal clearance of human pituitary gonadotropins (HPG) was studied in 18 normal ambulant postmenopausal subjects and in 32 hospitalized postmenopausal patients suffering from various diseases. Individual values for clearance were low, ranging from 0.04 to 0.43 ml. per minute. When the mean renal clearance in the ambulant group was compared with that in the hospitalized group, no significant difference was found. For both urine and plasma the mean levels of HPG were significantly higher in the ambulant subjects than in the hospitalized patients. It was apparent from the study that renal clearance of HCG was considerably higher than that of HPG and that the converse was true for plasma-urine concentration ratios. The

fact that a marked difference exists between the renal clearances of pituitary and placental gonadotropins is not surprising, but the exact mechanism by which gonadotropins are "cleared" by the kidney is not known and therefore no definite theory can be advanced to explain the observed difference.

J. Edward Hall

Doe et al.: Significance of Concentration of Non-protein-bound Plasma Cortisol, p. 1484.

The concentrations of total 17-hydroxycorticosteroid (17-OH-CS) and protein-bound 17-OH-CS were determined in plasma from various normal and abnormal subjects. The concentration of non-protein-bound 17-OH-CS was then calculated by subtraction of the protein-bound value from the total 17-OH-CS value. Elevated plasma total 17-OH-CS concentration in Cushing's syndrome was shown to be due entirely to an increase in the non-protein-bound 17-OH-CS fraction. Conversely, the elevated plasma total 17-OH-CS concentration in estrogen-treated males without signs of Cushing's syndrome was shown to be due entirely to an increase in the protein-bound 17-OH-CS. In women in the third trimester of pregnancy (with signs of mild adrenocortical hyperfunction) the levels of both protein-bound and non-protein-bound plasma 17-OH-CS were increased. It is suggested that the non-protein-bound plasma 17-OH-CS fraction is the immediately active form of cortisol. It probably has high activity because it is able to diffuse readily across capillaries and cell membranes.

J. Edward Hall

Krieger, Gabrilove, and Soffer: Adrenal Function in a Pregnant Bilaterally Adrenalectomized Woman, p. 1493.

The authors present a case of successful pregnancy in a patient who had undergone bilateral adrenalectomy for Cushing's syndrome. Studies of plasma and urinary steroids were performed before and after treatment, during pregnancy, and post partum. The observations suggest that the increased urinary excretion of aldosterone and the increased adrenal "responsiveness" to corticotropin seen in the normal pregnant subject require the presence of an intact adrenal gland and are not mediated through the placenta. The increase in the half-life of hydrocortisone in pregnancy is dependent on extra adrenal factors.

J. Edward Hall

No. 12, December, 1960.

*Landau, R. L., Plotz, E. J., and Lugibihl, K.: Effect of Pregnancy on the Metabolic Influence of Administered Progesterone, p. 1561.

*Rosenberg, E., and Engel, I.: The Influence of Steroids on Urinary Gonadotropin Excretion in a Postmenopausal Woman, p. 1576.

*Lanthier, A.: Urinary 17-Ketosteroids in the Syndrome of Polycystic Ovaries and Hyperthecosis, p. 1587.

Landau, Plotz, and Lugibihl: Effect of Pregnancy on Metabolic Influence of Administered Progesterone, p. 1561.

Three women in the fourth, seventh, and eighth months, respectively, of normal pregnancy were given courses of intramuscularly administered progesterone in a dose of 50 or 100 mg. per day. In none of them was there a detectable influence on protein metabolism. In one, the 100 mg. course appeared to influence a mild natriuresis; no loss of sodium occurred in the others. These results contrast with the moderate catabolic response and distinct natriuresis observed regularly in normal subjects. Approximately 50 mg. daily of administered progesterone had previously been shown to elicit a maximal catabolic response. The failure of progesterone to be catabolic in pregnant women was explained by the assumption that endogenous progesterone was already inducing its maximal catabolic influences. The mild and inconstant natriuretic responses may have resulted from an inability of administered progesterone to inhibit sufficiently the influence of the increased amount of aldosterone present during pregnancy.

J. Edward Hall

Rosenberg and Engel: Influence of Steroids on Urinary Gonadotropin Excretion in a Postmenopausal Woman, p. 1576.

Urinary excretion of human pituitary gonadotropin (HPG) was studied in a postmenopausal subject following the administration of methyl testosterone, conjugated estrogens, or norethisterone. HPG excretion was measured by the mouse uteri response, employing estrone as the standard reference material. Daily consecutive assays were made. Methyl testosterone in oral dosages of 5, 25, 50, or 100 mg. daily did not significantly alter HPG excretion. Conjugated estrogen in oral dosage of 0.25 mg. daily increased HPG excretion on the fifth day of ad-

ministration; there was a return to control levels immediately after withdrawal of medication. A dosage of 2.5 mg. of conjugated estrogens daily was tested twice with the following results: (1) HPG excretion was completely suppressed within 5 days; it rose to control values 13 days after cessation of medication; (2) HPG excretion was diminished on the seventh day, and the reduction was retained until 4 days after withdrawal of medication. Conjugated estrogen in a dosage of 5 mg. daily diminished HPG excretion on the last day of administration. Excretion rose to control levels on the 9th day after cessation of medication.

Estrogen sulfate in the daily dosage of 2.5 mg. did not significantly alter HPG excretion. Norethisterone in oral dosages of 5 and 10 mg. daily did not alter HPG excretion; 20 mg. daily caused diminution of HPG excretion on the sixth day of administration and there was a return to control levels 4 days after withdrawal of medication.

J. Edward Hall

Lanthier: Urinary 17-ketosteroids in the syndrome of polycystic ovaries and hyperthecosis, p. 1587.

The urinary 17-ketosteroid pattern was studied in 27 patients with polycystic ovaries and hyperthecosis (Stein-Leventhal syndrome). The three ketosteroid fractions were separated and measured. The mean value for total 17-ketosteroid was higher in the patients with Stein-Leventhal syndrome than in normal women, most of the difference being due to an increase in the androsterone plus etiocholanolone fraction. A study was made of the behavior of three urinary 17-ketosteroid fractions during stimulation with ACTH, suppression with 9 α -fluorohydrocortisone, stimulation with HCG estrogen therapy, and at intervals after bilateral wedge resection of the ovary. The results permit no conclusions regarding adrenocortical versus ovarian origin of this increased secretion of urinary androsterone plus etiocholanolone precursor.

J. Edward Hall

Vol. 21, No. 1, January, 1961.

*Daughaday, W. H., Holloszy, J., and Mariz, I. K.: The Binding of Cortisol and Aldosterone by Corticosteroid-Binding Globulin and the Estrogen-Induced Binding System of Plasma, p. 53.

*German, E., Horowitz, H., VandeWiele, R., and Torack, R. M.: Leydig Cell Tumor of the Ovary: Case Report and Review, p. 91.

Daughaday, Holloszy, and Mariz: Binding of Cortisol and Aldosterone by Corticosteroid-Binding Globulin and the Estrogen-Induced Binding System of Plasma, p. 53.

The binding of cortisol-4-C 14 and aldosterone-H3 by serum from pregnant or estrogen treated subjects is directly compared to the binding by serum from controlled subjects in a system of double equilibrium dialysis. Increased binding of cortisol-4-C 14 could be demonstrated by "estrogen" plasma under conditions of minimal cortisol loading only at 37° C. and not at 4° C. This difference of binding behavior is evidence that the binding sites induced by estrogen are qualitatively different from those on normal corticosteroid-binding globulin. The total concentration of cortisol-binding protein induced by estrogen may be two or three times greater than of corticosteroid-binding globulin. Under physiologic conditions of temperature, aldosterone-H3 is bound primarily by albumin, but, at 4° C., aldosterone-H3 is bound about equally by albumin and corticosteroid-binding globulin. At 4° C. the estrogen-induced binding system does not have appreciable affinity for aldosterone-H3.

J. Edward Hall

German et al.: Leydig Cell Tumor of the Ovary, p. 91.

The authors report a case of Leydig cell tumor of the ovary in a 60-year-old woman. The patient was originally admitted to the hospital for acute abdominal pain of 48 hours' duration, and an exploratory operation was performed revealing diverticulitis with perforation and generalized peritonitis. A colostomy was performed and the postoperative course was uneventful. It was noted at that time the patient presented an extremely masculine appearance so she was transferred to the Medical Service for further evaluation.

The patient had a receding hairline and an increase of facial and body hair. Her menstrual history was within normal limits and she had had a spontaneous menopause at age 53. She had been married 40 years without becoming

pregnant, though contraceptive procedures had never been employed.

Pertinent physical findings were those of a well-developed, elderly female with considerable hirsutism of the face, arms, legs, and trunk. There was a markedly receding hairline and spotty alopecia. The voice was female but there was some enlargement of the clitoris to about twice its normal size. The pelvis was filled with a hard, irregular mass which was located predominantly on the right side. It was impossible to differentiate uterus or adnexa from the mass.

Extensive laboratory investigation was done including the various electrolytes and extensive study for possible androgen excretion in abnormal amounts. However, there was no indication of any excessive androgens, the 17-ketosteroids measuring only 0.5 mg. The vaginal smear was atrophic.

The patient was ultimately reoperated on and a sigmoid resection with removal of the ovarian mass was performed. The ovarian tumor was reported as a firm, rubbery, nodular mass measuring 4.8 by 3.9 by 2.0 cm. It was gray-white and had the appearance of normal ovarian tissue. The microscopic examination revealed the tumor to consist of a large amount of pale eosinophilic homogenous stroma in which were varying sized islands of cells mostly arranged in small clusters. In places they tended to form cords and even rosettes. The nuclei of these cells were in general regular, and vesicular nucleoli were present. The cytoplasm of the cells was granular and deeply eosinophilic. This mass was interpreted to be a Leydig cell tumor of the ovary. This diagnosis was confirmed by the registry of ovarian tumors in Baltimore, Maryland.

Unfortunately, the patient developed a severe wound infection with ascending renal involvement and died in a progressive renal failure.

This case represents the fourteenth reported case of Leydig cell tumor of the ovary. It is of interest that, although this tumor undoubtedly was producing sufficient androgens to cause virilization, the androgenic material could not be demonstrated by the laboratory procedures used. This is not unusual in these cases since only 2 of 10 cases of the ones reported that had hormonal determinations had high androgen activity. The possible explanation for this discrepancy is discussed.

J. Edward Hall

Correspondence

Uterine isthmus

To the Editors:

I have read with interest the paper by Drs. Mann, McLarn, and Hayt on "The Physiology and Clinical Significance of the Uterine Isthmus" published on page 209 of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, February, 1961. Using a different technique, they fully confirmed the previously described variations in isthmic tone in the course of the normal menstrual cycle, this segment of the uterus becoming longer and narrower in the luteal phase of the cycle until the immediate premenstrual period when isthmic relaxation occurs.¹⁻³ They also concurred in the views that isthmic contraction during the luteal phase of the cycle and during pregnancy is of fundamental importance in protecting and supporting the growing ovum^{1, 4} and that isthmic hypotonia is a not infrequent cause of habitual abortion.^{2, 5} Their work and illustrations clearly demonstrate the validity of my original conclusions on the presence of two isthmic sphincters, one at the anatomic internal os and one at the histologic internal os, which I called the superior and the inferior isthmic sphincters, respectively.¹ In their isthmic repair operation they suggested placing two circlage sutures at sites which correspond to the position of these two sphincters.

It is surprising that in spite of their most significant findings Dr. Mann and his co-workers, throughout their paper, continued to speak of cervical incompetence rather than isthmic incompetence as a cause of habitual abortion.

The overwhelming evidence that it is the isthmus and not the cervix which is operative in the preservation of pregnancy has previously been discussed² and has been amply confirmed by Dr. Mann and his co-workers. Yet, unfortunately, the terms "cervical incompetence" and "incompetence of the internal os of the cervix"⁶ continue to be widely used.

In view of all the recently accumulated evidence on this subject it is obvious that the terms "cervical incompetence" and "incompetence of the internal os of the cervix" are misleading and should be discarded. The term "isthmic incompetence" which I introduced in 1958² is far more accurate and should, therefore, I think, be universally adopted.

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Items

Canadian Society for the Study of Fertility

The Eighth Annual Meeting of the Canadian Society for the Study of Fertility will take place at the Sheraton-Brock Hotel, Niagara Falls, Ontario, on Oct. 27 and 28, 1961.

Further information may be obtained by writing to the Secretary, Dr. George H. Arronet, Infertility Centre, Royal Victoria Hospital, Montreal, Quebec.

American Board of Obstetrics and Gynecology

The next scheduled examination (Part I), written, will be held in various cities of the United States, Canada, and military centers outside the Continental United States on Friday, Jan. 5, 1962.

Case reports are no longer required by this Board to complete the Part I examination.

In lieu thereof, all applicants and candidates for examination are required to submit a *duplicate certified typewritten list* of patients dismissed from each hospital during the preceding 12 months. This applies to new applicants,

candidates whose applications are reopened, and candidates requesting re-examination in Part I or Part II examination.

Lists of obstetric and gynecologic patients are to be made separately and must conform in all details to the sample format furnished upon request by the office of the executive secretary and treasurer.

Candidates are no longer required to bring a duplicate list of admissions to the Part II examination.

Current Bulletins may be obtained by writing to the executive secretary.

*Robert L. Faulkner, M.D.
Executive Secretary and Treasurer
2105 Adelbert Road
Cleveland 6, Ohio*

Society for the Scientific Study of Sex

The Fourth Annual Meeting of the Society for the Scientific Study of Sex will be held on Nov. 14, 1961, in the Barbizon Plaza, New York City. At the scientific session one panel will discuss "Sex in the Aging"; another, "Sexual Factors in Schizophrenia."